# THE ACTION OF CALCIUM IN HEART FAILURE

BY

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## INTRODUCTION

Since the days of Withering digitalis has held an honoured place in the treatment of cardiac failure. Occasionally, however, a patient is encountered who fails to react to this form of therapy. In Stobhill Hospital, among the numbers of patients with congestive heart failure, this type of refractoriness to digitalis is sufficiently common to justify the search for other forms of treatment.

In a preliminary investigation the relative merits of glucose and calcium were studied. The results with calcium were, however, so much better that attention was concentrated on this substance. The researches were conducted in the medical wards of Professor Morris at Stobhill Hospital, Glasgow, and in the Department of Materia Medica and Therapeutics, University of Glasgow.

I should like to express my indebtedness to Professor Morris for his constant encouragement no less than for his ready advice and co-operation, to Dr. Martin, Medical Superintendent of the Hospital, who has all along been interested in the investigations and has given me full scope for them, and to Mr. Rennie, technician, who has always been very willing to help me in every possible way.

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## PART I.

### RESUME OF PREVIOUS WORK.

(a) Physiological.

Ringer (44) was the first to discover that the frog's heart, perfused with a solution of common salt, soon lost its power of contraction, but that this did not occur if tap water instead of distilled water was used in the preparation of the solution; this he attributed to the presence of calcium salts in the tap water. In 1911 Mines (38) reported that the removal of calcium from the perfusing fluid was followed by a weakening of the heart beat and complete arrest within one to two minutes, while restoration of the calcium was followed immediately by an increase in the tone of the heart muscle and the force of contraction. Calcium was considered by Mines to be a "combining ion", i.e. one which owes its activity to the formation of a chemical compound with some essential constituent of the heart muscle.
The effect of calcium on cardiac activity was further clarified by Clark (14). He reduced the frog's heart to the "hypodynamic state" by perfusing for a few hours with Ringer's solution. In this heart he found a reduction both of the force of contraction and the rate of conduction. After the addition of calcium to the perfusing fluid no change was noted in the rate of conduction along the A.V. bundle or in the frequency of the heart beat, but there was observed a marked improvement in the force of the cardiac contraction.

When calcium was added to the perfusion fluid of the normal heart such improvement was again noted but to a much lesser degree. Clark, like Mines, considered calcium of the "combining ion" type and thought it probable that the cause of the "hypodynamic state" was the effect of perfusion in reducing the capacity of cardiac tissue to combine with calcium.

(b) Clinical.

It is obvious from the experimental work which has been recorded that calcium plays an important part in the maintenance of the normal heart beat. Since the early years of this century attempts have been made to make use of this element in the treatment of patients with cardiac disease. Lauder Brunton (10), in 1907, was the first to report good results. He used calcium chloride in doses of five to ten grains every four hours and advised its employment whenever there was evidence of ventricular weakness. For some time after this, however, calcium therapy in heart disease fell into disrepute. In this connection it is well to remember that with such small doses of calcium chloride little effect may be produced on the level of the serum calcium. With calcium lactate, a salt in much greater use than the chloride, the effect on the serum calcium is even less. Thus Denis and Minot (17) reported that there was no significant increase of serum calcium in seven normal subjects after the daily administration of ninety grains of the lactate for

periods of six to ten days. Presumably the action of calcium on the heart depends on its accumulation in the tissues of that organ which, in turn, depends on the elevation of the blood calcium. Accordingly, the mere retention of lime by the body will not necessarily produce an effect on the heart unless the serum calcium has been increased. Since 1920 this has been recognised by clinicians and pharmacologists whose efforts have been directed to obtaining the cardiotonic action of calcium by the parenteral, especially the intravenous, administration of its salts. It will be convenient now to classify and consider the results of previous workers with reference to various individual phenomena.

The Effect of Calcium Salts upon Heart Rate. It was reported by Petzetakis (42) that the intravenous administration of calcium chloride in doses of ½ to 1 gram led to a slowing of the heart rate. He found that benefit was derived from this form of therapy in the following three types of cardiac disease: (a) Ventricular extrasystoles, (b) Tachycardia where other therapeutic measures such as digitalis and ouabain had failed to bring relief, and (c) Complete arrhythmia where quinidine, ouabain, and digitalis had proved unsuccessful. In these cases the use of calcium was followed by a reduction in the heart rate and abolition of any irregularity that might previously have been noted. The slowing effect of an intravenous injection of 10% calcium

chloride was also described by Billigheimer ( 4). The slowing lasted from twenty-five to thirty minutes and was more marked the more rapid the original rate. From the fact that tachycardia produced by atropine administration was practically uninfluenced by calcium, he argued that calcium acted on the vagus nerve endings which, it is well known, are paralysed by atropine. Brull ( 9 ), reporting similar results, showed that the bradycardia was not the result of a reflex stimulated by an increase of arterial blood pressure since a similar effect was produced when the blood pressure was lowered. Since section of the vagi as well as atropinisation prevented the slowing effect, he concluded that the bradycardia produced by calcium in moderate doses was due to a stimulation of the vagus centre. Edwards and Page (18) used parathyroid extract to raise the percentage of calcium in the serum. They obtained a preliminary slight tachycardia which was followed by a very marked slowing. As the bradycardia reached its maximum there was often noted a marked irregularity of cardiac rhythm. Lloyd (32) described the effects on himself of an intravenous injection of 4 c.cs. of a 10% solution of calcium chloride. Dizziness, collapse, great respiratory embarrassment, dilatation of the pupil, and some generalised muscle spasm resulted; urgent remedial measures had to be undertaken and recovery ensued in four to five minutes. Electrocardiograms showed that the rate of the heart had been reduced by one half. The rate of injection is not reported

but the acutely unpleasant effects were in all probability due to the fact that the solution was injected too rapidly. Liebermann (31) states that while very large amounts of calcium can be given if the rate of administration is sufficiently slow, even small doses may prove fatal when given rapidly. According to McGuigan and Higgins (39) the degree of calcium bradycardia depends, to a large extent, on the rate of injection.

The Effect of Calcium Salts upon Blood Pressure. Whereas it seems that all writers are agreed as to the slowing action of calcium on the heart rate, there is not the same uniformity of opinion with regard to its effect on blood pressure. Singer (48), writing in 1921, claimed that intravenous calcium lowered the blood pressure. Brull (9), working on dogs, maintained that calcium raised the pressure as a result of peripheral vasoconstriction in association with a direct action on heart muscle. Only when extreme bradycardia was produced did he find that the pressure was lowered. Walter and Bowler (52), however, stated that no significant change of blood pressure was produced. In a series of ten cases the blood pressure was raised in eight and unchanged in two. In the former group the maximum elevation was twenty millimetres of mercury about five minutes after the injection, and the pressure returned to normal or even slightly below normal after forty to sixty minutes. Edwards and Page (18) found that in association with considerable slowing the blood pressure fell. Bower and Mengle (6) stated that

there was a tendency to lowering of the blood pressure which was less marked the slower the injection was given.

The Effect of Calcium Salts upon Diuresis. Singer (48), in 1921, found that the intravenous administration of calcium salts led to a temporary diuresis in both cardiac and renal cases. Cheinisse (12), in the following year, claimed that calcium aided the diuretic action of digitalis in cases of cardiac failure with oedema. Blum ( 5 ) was of the opinion that calcium chloride had a powerful diuretic effect but this he attributed to the chloride ion. Loewenberg (33) found that small doses of calcium, sufficient to act in a cardiotonic capacity, had no diuretic effect, while larger doses caused a marked increase in urinary volume. He concluded that the two actions had different mechanisms. Brull ( 9 ) was of the opinion that calcium had no diuretic action and considered indeed that the output may even be lessened as a result of a vasoconstrictor effect on the peripheral arterioles including the renal vessels. Segall and White (47), in 1925, concluded from their results that in cases of cardiac failure with oedema, in which the ordinary methods of treatment have not resulted in a satisfactory diuresis, calcium chloride may with advantage be employed as a diuretic. They gave calcium chloride by mouth to seventeen patients and found considerably increased diuresis in eight of them, slight increase in five and no increase in four. The diuretic effect, when present, was

not associated with any circulatory change and in all probability was the result of the well known acidotic effect of calcium chloride.

(c) The Mode of Action of Calcium Salts upon the Heart.

The mode of action of calcium has been much debated. Most workers are agreed that it acts directly on heart muscle but there is less uniformity of opinion as to whether there is any effect exerted through the nervous system.

Stewart (50), by a method of moving X-Ray photographs, obtained direct measurements of the contracting power of the heart after intravenous injection of 10% calcium chloride, and thus demonstrated the effect on cardiac muscle. Schiff, Busquet and Pachon (46) found that the inhibitory effect of vagus stimulation disappeared in the absence of calcium. This was disputed by Brine (8) who worked on the turtle heart. Brull (9) found that calcium strengthened the contraction of the isolated heart of the dog. He further reported that section of the vagus nerves in the neck or their paralysis by atropine prevented the onset of bradycardia or put an end to it - unless large amounts of calcium were given; if toxic doses were given even though the vagus nerves had been sectioned, there was slowing which often progressed to complete arrest. This was attributed to auriculo-ventricular dissociation, preventing the influence of atropine on the ventricular beat. According to Billigheimer (4), atropine tachycardia

was practically uninfluenced by calcium while a very slow vagus pulse was not further slowed by calcium. Popescu-Inotesti (43) stated that calcium stimulated either the sympathetic or the parasympathetic cardiac nerves depending on the amount of the drug given. In small doses, from .1 to 1 gram intravenously, it caused stimulation of the sympathetic as shown by increase in heart rate, rise in blood pressure, dilatation of the pupil, raised blood sugar, and increased respiratory rate; while in larger doses - between 1.5 and 4 grams - stimulation of the parasympathetic resulted as shown by slowing of the heart rate, contraction of the pupil, fall in blood sugar, and slower respiratory rate. Berliner ( 2 ) quoted Rothberger and Winterberg who were of the opinion that the effect of calcium was exerted not through the nervous system but directly on the ventricular muscle. These workers did not observe any effect upon the sinus and A. - V. nodes. Berliner himself, after reviewing the literature available, concluded by stating that it was still doubtful as to whether calcium stimulated the sympathetic nerves or the vagi.

It is obvious that the relationship between calcium and vagus action is not a simple one. Thus Hagan and Ormond (24) found that the effect of calcium withdrawal was augmented by the presence of potassium. Furthermore the extent to which the calcium is diminished plays a part. Cazzola (11) showed that a moderate decrease of calcium actually increased the excitability of the vagus which was markedly reduced by

a further diminution of calcium. As might be expected an increase of calcium restores the irritability of the vagus which has previously been depressed by magnesium (Auer & Meltzer) (1).

Other workers suggest that calcium antagonises both the toxic action of sodium and the inhibitory effect of potassium. Withdrawal of calcium from the perfusing fluid would therefore lead to a predominance of the potassium effect since this ion predominates in muscle tissue. Accordingly the rhythmic contractions of the heart muscle would rapidly disappear (Sollman) (49). Indeed the rapidity with which the normal contractility of the myocardium is abolished by a calcium-free perfusing fluid suggests that this effect is due to an action on the plasma membrane (Sollman). Sollman further reports that in the perfused heart of the frog, absence of calcium from the perfusing fluid does not appear to influence the action of drugs such as epinephrine, strophanthine, or veratrine.

(d) The Relationship of Calcium and Digitalis.

The summary of the literature on the pharmacology of calcium is sufficient to indicate many similarities to the action of digitalis. Loewi (34) stressed the close relationship between the actions of calcium and digitalis on the heart and went so far as to suggest that the main effect of the digitalis glucosides was obtained by sensitising the heart muscle to calcium.

This view was supported by Daniélopopu (16) who thought

that small doses of calcium should be given intravenously along with digitalis. Singer (48), who found that intravenous calcium caused a temporary diuresis in cardiac patients along with a temporary strengthening of the heart action, slowing of rate, and lowering of blood pressure, states that the best results were obtained by giving the two drugs simultaneously. It was the opinion of Cheinisse (12) also that calcium potentiated the action of digitalis in cases of cardiac failure with oedema. From these findings Loewenberg (33) concluded that the diuretic effect was not merely the result of increased tone of the cardiac muscle. Loewenberg noted that while small doses of calcium were sufficient to produce increased power of contraction of the heart they had no effect on the urinary output, for which much larger doses were necessary: he stated, indeed, that the cardiotonic and diuretic actions were not related.

According to Billigheimer (4) the actions of calcium and digitalis are very similar, except that the effect of the former is more transient. Digitalis, he found, produced a rise in blood calcium and the degree of reaction to digitalis was in proportion to this increase of calcium in the blood. Patients with a low blood calcium tolerated less digitalis than those in whom the concentration of calcium in the blood was high. Billigheimer further found that where digitalis did not produce any therapeutic effect

or acted in a paradoxical manner, calcium acted similarly. The two drugs, he observed, were alike in their action on vessels and on blood pressure, and they potentiated one another; in association they proved of value in many forms of decompensation and absolute arrhythmia. No ill effects resulted from using the two in combination, a procedure, indeed, which was considered advisable for the sake of the combined action. A further recommendation was that calcium should be given by itself at any time when digitalis was badly borne.

The view that digitalis sensitised the heart for calcium as propounded by Loewi and supported by Singer and Danielopopu did not find favour with Mandelstamm (36). In 1926, working on the rabbit, he found that although calcium was essential for the contractility of heart muscle and the effect of strophanthine was enhanced by increasing the calcium content, strophanthine did not sensitise the heart to calcium and indeed that its action was independent of the presence of calcium. In 1927, Fischer (19), working on frogs, found that the action of digitoxin was not affected by the presence or absence of calcium but that if calcium was given immediately after the digitoxin effect appeared, comparatively small doses of calcium were sufficient to produce tonic contraction of the heart. Fischer concluded that digitoxin sensitised the heart for calcium but that the sensitisation was not specific since

the digitoxin had merely made the heart more irritable and any further stimulus would have had the same effect as calcium. This view was supported by Cloetta (15).

Nyiri and Dubois (41) found that (a) the digitalis action could take place in the absence of calcium; (b) increase of the calcium level to three or four times the physiological concentration reinforced and accelerated the effect of digitalis on the heart muscle, and (c) digitalis enhanced the effect of an increased calcium concentration of the blood. They concluded that while calcium and digitalis are not essentially related in their pharmacological actions, yet the similarity of their effects on the heart justifies their combined use in therapeutics.

Thus while the hypothesis of Loewi and Danielopopu was gradually disproved and it was realised that the action of digitalis was not merely to sensitise the heart to calcium, the synergism of calcium and digitalis received further corroboration. Gold and Edwards (21) demonstrated this synergism quantitatively by producing hypercalcaemia in dogs and finding that this reduced the minimum lethal dose of ouabain.

Liebermann (31), 1933, was of the opinion that calcium and digitalis act not synergically but additively and that they had a similar action taking effect at dissimilar speeds. McGuigan and Higgins (39), using dogs,

gave digitalis - 10% tincture in 25% alcohol - and calcium gluconate, in the following ways :- (a) digitalis followed by calcium, (b) calcium followed by digitalis, (c) digitalis and calcium alternately.

They found that calcium gluconate in large and small doses had no perceptible action on digitalis other than an additive toxic effect. They summarised their results by reporting that calcium acts on the heart in a similar manner to digitalis and that the action of these two drugs given together is additive; that calcium may be administered intravenously in quite large amounts if given slowly and when so given that there is no specific danger in its administration after digitalis other than an additive effect. For slow administration they suggested giving 10 c.cs. of 10% calcium gluconate in at least two minutes at a uniform rate. Nahum and Hoff (40) found the dose of calcium chloride necessary to produce momentary cardiac arrest in the rabbit; they found no change in the strength of the action of the salt after strong doses of digitalis. Golden and Brams (22), on the other hand, found that after intravenous digitalis the minimum lethal dose of calcium was markedly diminished. La Barre and Van Heerswynghels (29) in 1939, reported that digitalised cats were more than ordinarily susceptible to the action of calcium: this they found by obtaining direct tracings of the heart beat, and by electrocardiogram tracings. The M.L.D. of calcium

gluconate for cats who had been digitalised was 60%. They conclude that the additive effects of the two substances may cause serious cardiovascular upset, especially in those subjects already showing signs in the electrocardiogram of digitalis poisoning.

## PART II.

## THE PRESENT INVESTIGATION.

### (a) General.

From preliminary investigations it soon became apparent that in some patients with congestive heart failure calcium therapy was of considerable value. As a result it was decided to study the action of calcium as a therapeutic agent with reference to cardiac decompensation. For this purpose patients were chosen who had failed to respond satisfactorily to the exhibition of digitalis. In some instances, however, where it was desired to study the effect of calcium uninfluenced by the presence of digitalis, patients were chosen who had not received any of the digitalis glucosides for at least one month previously. The preparation used in all cases was a solution of 10% calcium gluconate. The methods adopted throughout the investigation are detailed in the various sections. These are arranged for convenience in the following order. In the first place an account is given of the level of serum calcium in patients with cardiac failure, and the influence of digitalis therapy on this level. It is hoped that these results are in themselves sufficiently conclusive to support the view advanced by previous workers that calcium plays an important part in maintaining normal heart function, and that it is in some way associated with digitalis in the restoration of power to the failing heart. The succeeding sections are

occupied with a description and critical analysis of the clinical pharmacology of calcium as far as concerns cardiac decompensation. A small section follows on the toxic effects of calcium with special reference to its combination with digitalis. Finally the clinical results of calcium therapy are given in detail and discussed, and an attempt is made from the evidence presented in the thesis to draw conclusions as to the indications and dangers of calcium therapy in cardiac failure.

(b) The Calcium Content of the Serum

(1) In Heart Failure.

If calcium plays an important part in the maintenance of normal cardiac function, it might be expected that variations of serum calcium outwith normal limits would not be uncommon in patients with heart failure. To test this hypothesis the serum calcium was estimated in a number of patients without cardiac dysfunction and in some with heart failure. Blood was withdrawn when the subject was in the post-absorptive state. The calcium was estimated by the method of Kramer and Tisdall (27).

In the group of twenty-three patients without evidence of cardiac failure the serum calcium varied between 9.6 and 11.7 mgrms. % with a mean value of 10.5 mgrms.%. In thirty patients with gross cardiac decompensation the concentration of calcium in the serum varied from 8.0 mgrms.% to 13.5 mgrms.% with a mean value of 10.6 mgrms.%. Although the average values are practically the same, the limits are much wider in the group with cardiac failure.

Table (1) shows the serum calcium value of each of the thirty patients with cardiac decompensation with the essential features of the heart failure as presented by each patient.

TABLE 1.

| Name | Oed. | Cyan. | Dyspn. | Serum Calcium. |
|---|---|---|---|---|
| A. | +++ | | | 9.1 |
| B. | ++ | | | 11.5 |
| C. | ++ | | | 8.5 |
| D. | | ++ | + | 11.6 |
| E. | | + | + | 10.1 |
| F. | | ++ | | 9.5 |
| G. | | ++ | | 8.6 |
| H. | ++ | | | 10.3 |
| I. | | + | | 9.3 |
| J. | +++ | | | 8.9 |
| K. | ++ | + | | 10.2 |
| L. | ++ | | | 13.5 |
| M. | ++++ | | + | 11.0 |
| N. | ++ | | + | 11.0 |
| O. | +++ | + | + | 11.6 |
| P. | ++ | + | | 8.6 |
| Q. | + | ++ | | 10.9 |
| R. | +++ | | + | 10.6 |
| S. | ++ | | + | 8.0 |
| T. | +++ | + | + | 10.4 |
| U. | + | ++ | + | 9.8 |
| V. | + | ++ | | 10.0 |
| W. | | ++ | | 11.2 |
| X. | | + | + | 12.7 |

TABLE 1 (Contd.)

| Name | Oed. | Cyan. | Dyspn. | Serum Calcium |
|---|---|---|---|---|
| Y. | | +++ | + | 13.0 |
| Z. | | ++ | | 12.8 |
| AB. | | + | | 11.5 |
| CD. | | ++ | ++ | 11.7 |
| EF. | | + | + | 11.5 |
| GH. | | + | | 11.8 |

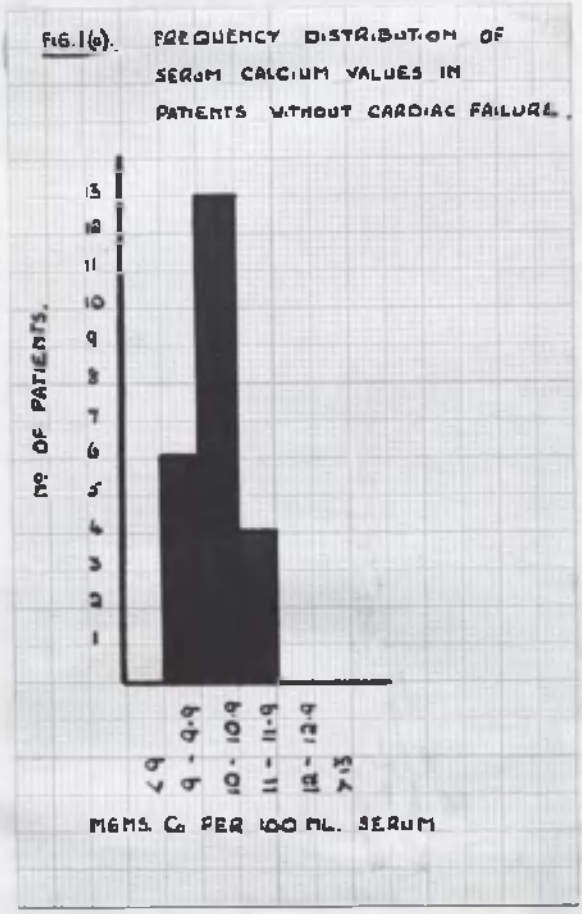
The following may be briefly summarised from these results :-

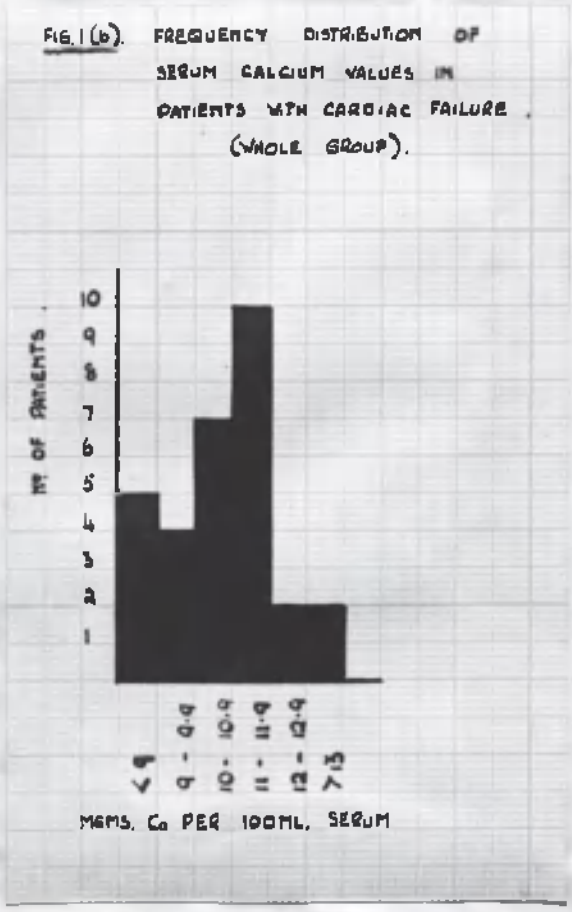
TABLE 2.

Mean Values for Serum Calcium in Mgrms.% in Patients with Heart Failure.

| | | |
|---|---|---|
| Whole Group 10.6 | With Oedema 10.2 | Without Oedema 11.2 |
| Whole Group 10.6 | With Cyanosis 10.8 | Without Cyanosis 10.2 |
| Whole Group 10.6 | With Dyspnoea 11.0 | Without Dyspnoea 10.3 |

The distribution of values for serum calcium in patients without evidence of cardiac failure and in those with cardiac failure is shown graphically, Figs. 1 (a) and 1 (b).




The graphs show that, though the average values for the two groups are the same, the distribution varies markedly. They suggest that in heart failure there is a disturbance in the metabolism of calcium as far as the regulation of serum calcium is concerned. The next two graphs show the distribution in cardiac failure with and without oedema, Figs. 2 and 3.

FIG. 2. FREQUENCY DISTRIBUTION OF SERUM CALCIUM VALUES IN PATIENTS WITH CARDIAC FAILURE. (GROUP WITH OEDEMA).

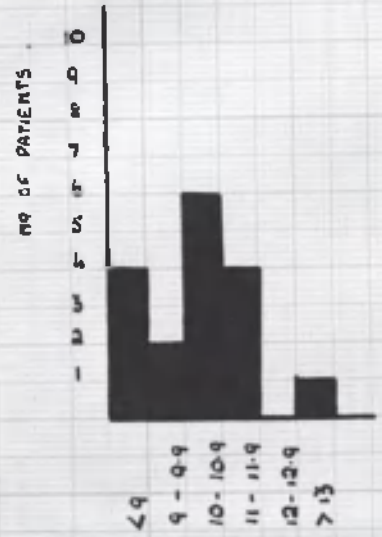
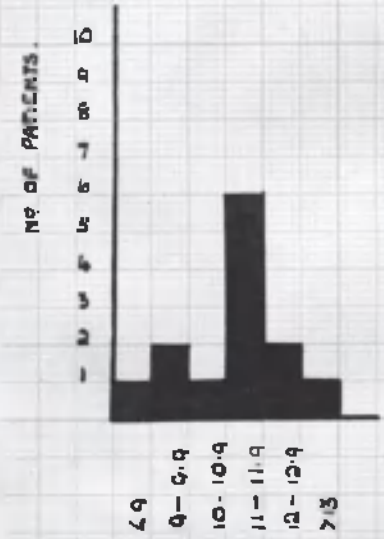



FIG. 3. FREQUENCY DISTRIBUTION OF SERUM CALCIUM VALUES IN PATIENTS WITH CARDIAC FAILURE. (GROUP WITHOUT OEDEMA).




It will be noted from Table 2 that in patients with cardiac failure those with evidence of oedema had a lower mean value for serum calcium than those without oedema; this is further shown by Figs. 2 and 3. Statistically, however, this difference was not significant as it was found that the odds were only ten to one that it was not a chance observation. The mean values for the groups with cyanosis and dyspnoea were higher than for the patients without these manifestations but in neither case was the difference significant.

(2) The Effect of Digitalis Medication.

It has been claimed that digitalis therapy exerts an influence on the action of calcium on the myocardium. Billigheimer ( 4 ), indeed, maintains that digitalis produces a rise in serum calcium. In order to investigate this point the serum calcium was estimated in twenty patients with cardiac decompensation before and during a course of digitalis treatment. The results are given in Table 3.

TABLE 3.

Showing Effect of Digitalis Therapy on the Level of Serum Calcium

| Name | Days on Digitalis | Serum Calcium mgrms.% | | Change in Serum Calcium mgrms.% |
|---|---|---|---|---|
| | | Before Digitalis Therapy | During Digitalis Therapy | |
| A. | 20 | 9.1 | 10.4 | +1.3 |
| B. | 109 | 11.5 | 12.8 | +1.3 |
| C. | 20 | 10.1 | 10.2 | +0.1 |
| D. | 21 | 9.5 | 10.7 | +1.2 |
| E. | 8 | 8.6 | 11.6 | +3.0 |
| F. | 85 | 8.9 | 11.3 | +2.4 |
| G. | 13 | 10.2 | 12.7 | +2.5 |
| H. | 17 | 11.0 | 12.2 | +1.2 |
| I. | 13 | 11.0 | 11.0 | 0.0 |
| J. | 23 | 11.2 | 12.1 | +0.9 |
| K. | 36 | 11.6 | 9.9 | -1.7 |
| L. | 56 | 8.6 | 8.9 | +0.3 |

TABLE 3 (Contd.)

| Name | Days on Digitalis | Serum Calcium mgrms.% | | Change in Serum Calcium mgrms.% |
|---|---|---|---|---|
| | | Before Digitalis Therapy | During Digitalis Therapy | |
| M. | 15 | 10.6 | 10.5 | -0.1 |
| N. | 30 | 11.5 | 11.9 | +0.4 |
| O. | 79 | 8.0 | 10.4 | +2.4 |
| P. | 123 | 10.0 | 11.3 | +1.3 |
| Q. | 33 | 9.3 | 10.0 | +0.7 |
| R. | 37 | 10.4 | 11.8 | +1.4 |
| S. | 33 | 10.7 | 10.7 | 0.0 |
| T. | 19 | 10.0 | 10.2 | +0.2 |

These results may be summarised as follows :-

TABLE 4.

| Decrease | No Change | Increase mgrms.% | | |
|---|---|---|---|---|
| | | .5-1.5 | 1.5-2.5 | 2.5 |
| 1 | 7 | 8 | 3 | 1 |

Any increase of serum calcium less than 0.5 mgrms.% was not considered significant and has been included in the "no change" column. Of the twenty patients investigated, twelve showed a definite increase in serum calcium, seven no change, and one a reduction. No explanation can be offered as to the reduction of 1.7 mgrms.% observed in patient K. No relationship could be detected between the

actual or percentage increase in serum calcium and the original values, or dosage of digitalis either daily or total.

The findings presented in this section support the view of Billigheimer that a course of digitalis therapy in cardiac failure is associated with an increase in serum calcium concentration. This increase did not necessarily indicate clinical improvement and thus did not help in forming an idea as to prognosis. The findings also raise the interesting pharmacological problem as to whether part of the digitalis effect may not be due to a mobilisation of calcium ~~and~~ rendering it available to the myocardium where it can exert a tonic effect. A consideration of the actions of calcium (as will be described subsequently) and digitalis suggests that there may be some foundation for this hypothesis. Both drugs slow the heart rate, exert in some cases at any rate a tonic effect on the heart muscle, and have some influence on diuresis. In a few patients calcium has been reported to produce coupling of heart beats - such a case has been encountered in the course of the present work. The great differences in the action of the two drugs are (1) the time factor of onset of effect and duration and (2) the influence of rhythm. The calcium effect upon the heart can be demonstrated almost immediately but is generally transient. The digitalis effect, on the other hand, takes longer to become apparent and lasts much longer. Calcium appears to act much more

powerfully in patients with regular heart rhythm,whereas the ideal type of patient for the exhibition of digitalis is one with auricular fibrillation.

In eleven patients with cardiac failure it was found possible to obtain blood for the estimation of serum calcium within a few minutes to a few hours of death. None of the patients had received calcium or parathyroid therapy. For comparison I had the opportunity of determining the concentration of calcium of the serum under similar conditions in seven patients who died as a result of some disease not associated with the cardiovascular system. The results are given in Tables 5 and 6.

TABLE 5

Showing the Level of Serum Calcium in Patients Dying from Heart Failure.

| Name | Date | Serum Calcium mgrms. % |
|---|---|---|
| A. | 27/6/38<br>4/7/38 (D) | 8.6<br>11.6 |
| B. | 30/6/38<br>4/7/38 (D) | 10.3<br>8.1 |
| C. | 13/7/38 (D) | 13.5 |
| D. | 22/7/38 (D) | 12.7 |
| E. | 17/9/38<br>1/10/38<br>17/10/38 (D) | 10.6<br>10.5<br>6.2 |

TABLE 5 (Contd.)

| Name | Date | Serum Calcium mgrms.% |
|---|---|---|
| F. | 13/10/38 (D) | 11.7 |
| G. | 22/12/38 (D) | 8.9 |
| H. | 28/12/38 (D) | 8.6 |
| I. | 30/1/39 (D) | 8.8 |
| J. | 1/2/39 (D) | 8.2 |
| K. | 6/3/39 (D) | 12.8 |

TABLE 6

| Name | Disease | Date | Serum Calcium mgrms. % |
|---|---|---|---|
| A. | Hemiplegia | 23/12/38(D) | 10.2 |
| B. | Phthisis | 7/11/38(D) | 10.7 |
| C. | Lobar Pneumonia | 8/9/38 (D) | 9.8 |
| D. | Amyloid Disease | 30/1/39(D) | 9.7 |
| E. | Cerebral Haemorr-hage. | 6/10/39(D) | 9.3 |
| F. | Carcinoma of Oesophagus | 3/11/39(D) | 10.1 |
| G. | Diabetic Gangrene | 2/12/39(D) | 10.7 |

(D) .... Date of Death.

In the cardiac group it is obvious that the level

for serum calcium on the day of death was in every case outwith the usually accepted normal limits of nine to eleven mgrms.% and which were found to hold good for the non-cardiac group. In three instances (A, B, E, table 5) I had the opportunity of comparing these ante-mortem results with the values obtained in the same patients some days previously. In all three there was noted a great swing, in twocases downwards and in one upwards. These findings, although few in number, support the other evidence that in heart failure there is a disturbance in the metabolism of calcium as far as the regulation of serum calcium is concerned.

## (c) General Effect of a Single Intravenous Injection of Calcium Gluconate.

The effect of intravenous administration of calcium gluconate on the various manifestations of cardiac failure and the general condition of the patient are dealt with in the appropriate sections. Here it is desired to give a brief account of the subjective disturbances following a single injection of calcium gluconate. The first sensation experienced by the patient is a feeling of heat in the mouth, sometimes associated with a metallic taste. Rather later a sense of heat is complained of at the site of injection; this rapidly spreads over the surface of the body. In no case was the sensation more than unpleasant. A fact which quickly became manifest was that the intensity of the sensation of heat was proportional to the rate of injection. The more rapidly the calcium gluconate was given, the more marked was the sense of discomfort. This prompted me to determine the optimal rate of injection. It is obvious that the drug should be administered as quickly as possible so that the psychological disturbance of an intravenous injection is minimal. It soon became apparent that if at least two minutes are taken for the administration of 10 c.cs. of the 10% solution and the injection given as smoothly as possible, there is little if any complaint from the patient. This optimal rate of administration was found by trial and error when, a few

years ago, use was made of the drug in a period spent at obstetrical work. In some cases a very slight flushing of the cheeks has been visible, while in others a slight and very transient increase in the respiratory rate has been noted. The increase in the rate of breathing has not exceeded that which is frequently found during any intravenous therapy and is almost certainly to be ascribed to very natural excitement. There were no febrile reactions which are sometimes met with after intravenous injections of saline and glucose. It is the present routine not to give calcium unless at least four days have elapsed since the cessation of digitalis therapy. This last point, however, will be discussed later in the section dealing with toxic manifestations. Meanwhile it can be stated that no untoward reaction has been encountered during and after injections of calcium gluconate, in patients, performed in the method described above. It seems reasonable, therefore, to assume that the careful intravenous administration of 10% calcium gluconate is a safe procedure.

(d) Effect of Calcium on the Heart Rate.

The heart rate was determined by auscultation at the apex. Care was taken to prevent any preliminary excitement by getting the patient accustomed to all the paraphernalia of an intravenous injection. The heart rate was taken continuously for ten minutes prior to the injection, throughout the injection, and for five minutes afterwards. Thereafter counts were made at varying intervals until the rate reached its previous level.

Of twenty-six patients so examined, it was found that twenty reacted to the calcium gluconate by a slowing of from six to seventy-eight beats per minute. The other six showed no change. Details are given in Table 7 of those investigations where slowing was demonstrated. The effect of the intravenous injection of calcium gluconate was investigated in each case on several different days but in the Table only that day is shown on which the maximal change was produced. The duration of slowing is tabulated as twenty-four hours if the rate is still slower on the day succeeding the injection than it was before the injection.

TABLE 7

| Name | Date | Rhythm | Heart Rate Before Calcium | Maximal Slowing in Rate | | | Duration of Slowing. |
|---|---|---|---|---|---|---|---|
| | | | | Beats/ Min. | % of Original Rate. | Time After Calcium | |
| A. | 28/2/38 | Reg. | 88 | 13 | 14.7 | 1 Hour | 24 Hours |
| B. | 5/3/38 | Reg. | 105 | 18 | 17.1 | 7 Mins. | 24 Hours |
| C. | 21/3/38 | Reg. | 162 | 78 | 48.1 | 6 Mins. | 3 Hours |
| D. | 25/3/38 | Reg. | 78 | 12 | 15.4 | 5 Mins. | 24 Hours |
| E. | 22/4/38 | Reg. | 96 | 24 | 25 | 1 Hour | 24 Hours |
| F. | 11/3/38 | Irreg. | 131 | 13 | 10 | 5 Mins. | 24 Hours |
| G. | 9/2/38 | Irreg. | 96 | 9 | 10 | 5 Mins. | 1 Hour |
| H. | 31/3/38 | Irreg. | 87 | 19 | 21 | 7 Mins. | 11 Mins. |
| I. | 5/4/38 | Irreg. | 120 | 12 | 10 | 6 Mins. | 50 Mins. |
| J. | 7/2/38 | Reg. | 88 | 34 | 38 | 5 Mins. | 24 Hours |
| K. | 14/3/38 | Irreg. | 79 | 28 | 35.5 | 7 Mins. | 1 Hour |
| L. | 9/4/38 | Irreg. | 156 | 21 | 13 | 10 Mins. | 55 Mins. |
| M. | 13/3/38 | Reg. | 142 | 52 | 36.6 | 1 Hour | 24 Hours |
| N. | 17/3/38 | Reg. | 106 | 28 | 26.4 | 1 Hour | 24 Hours |
| O. | 11/2/38 | Reg. | 141 | 59 | 41 | $1\frac{3}{4}$ Hours | $3\frac{3}{4}$ Hours |
| P. | 15/3/38 | Reg. | 112 | 21 | 19 | 4 Mins. | 30 Mins. |
| Q. | 21/4/38 | Reg. | 96 | 15 | 15.5 | 5 Mins. | 5 Hours |
| R. | 3/5/38 | Irreg. | 80 | 6 | 7.5 | 2 Mins. | 10 Mins. |
| S. | 1/2/38 | Reg. | 102 | 20 | 20 | 20 Mins. | 24 Hours |
| T. | 25/3/38 | Irreg. | 96 | 8 | 8.3 | 5 Mins. | 1 Hour |

The time of maximal slowing varied from patient to patient as shown in the preceding table. But it also varied in the same patient from day to day, and this is shown in the following table, Table 8. For this purpose, the different daily investigations on a few of the patients are shown in full :-

TABLE 8

Showing Variation of Degree and Time of Maximal Slowing and Total Duration of Slowing in Same Patient from Day to Day.

| Name | Date | Original Heart Rate. | Maximal Slowing | | | Total Duration of Slowing. |
|---|---|---|---|---|---|---|
| | | | Beats/ Min. | % of Original Rate. | Time | |
| A. | 25/2/38 | 90 | 4 | 4.4 | 5 Mins. | 10 Mins. |
| | 28/2/38 | 88 | 13 | 14.7 | 1 Hour | 24 Hours |
| | 1/3/38 | 72 | 2 | 2.9 | 5 Mins. | 6 Mins. |
| | 2/3/38 | 70 | 0 | - | - | - |
| G. | 20/3/38 | 162 | 78 | 48.1 | 6 Mins. | 3 Hours |
| | 22/3/38 | 162 | 9 | 5.5 | 5 Mins. | 12 Mins. |
| D. | 25/3/38 | 78 | 12 | 15.4 | 5 Mins. | 24 Hours |
| | 26/3/38 | 69 | 3 | 4.3 | 5 Mins. | 12 Mins. |
| | 27/3/38 | 75 | 9 | 12 | 5 Mins. | 24 Hours |
| | 30/3/38 | 69 | 9 | 13 | 5 Mins. | 24 Hours |
| E. | 17/4/38 | 90 | 21 | 23.3 | 1 Hour | 24 Hours |
| | 18/4/38 | 72 | - | - | - | - |
| | 19/4/38 | 90 | - | - | - | - |
| | 20/4/38 | 78 | 3 | 3.8 | 5 Mins. | 12 Mins. |
| | 21/4/38 | 80 | - | - | - | - |
| | 22/4/38 | 96 | 24 | 25 | 1 Hour | 24 Hours |
| | 23/4/38 | 74 | 2 | 2.5 | 5 Mins. | 10 Mins. |
| | 24/4/38 | 72 | - | - | - | - |
| H. | 29/3/38 | 105 | 0 | 0 | - | - |
| | 30/3/38 | 87 | 0 | 0 | - | - |
| | 31/3/38 | 87 | 19 | 21 | 7 Mins. | 11 Mins. |

TABLE 8 (Contd.)

| Name | Date | Original Heart Rate. | Maximal Slowing | | | Total Duration of Slowing. |
|---|---|---|---|---|---|---|
| | | | Beats/ Min. | % of Original Rate. | Time | |
| J. | 7/2/38 | 88 | 34 | 38 | 5 Mins. | 24 Hours |
| | 8/2/38 | 63 | - | - | - | - |
| | 9/2/38 | 72 | 1 | 1.3 | 3 Mins. | 5 Mins. |
| | 10/2/38 | 72 | 3 | 4.1 | 5 Mins. | 10 Mins. |
| | 11/2/38 | 96 | 30 | 30.1 | 2 Mins. | 24 Hours |
| | 12/2/38 | 78 | 27 | 34.6 | 7 Mins. | 11 Mins. |
| P. | 15/3/38 | 112 | 21 | 19 | 4 Mins. | 30 Mins. |
| | 16/3/38 | 112 | 17 | 15.1 | 8 Mins. | 45 Mins. |
| T. | 24/3/38 | 96 | 6 | 6.2 | 10 Mins. | 30 Mins. |
| | 25/3/38 | 96 | 8 | 8.2 | 5 Mins. | 1 Hour |

The duration of the slowing varied from five minutes to more than twenty-four hours. The time relationships of the reduction of heart rate in a few cases are shown in the following figures, Figs. 4, 5, 6, and 7. It is evident that the slowing is not a smooth fall.

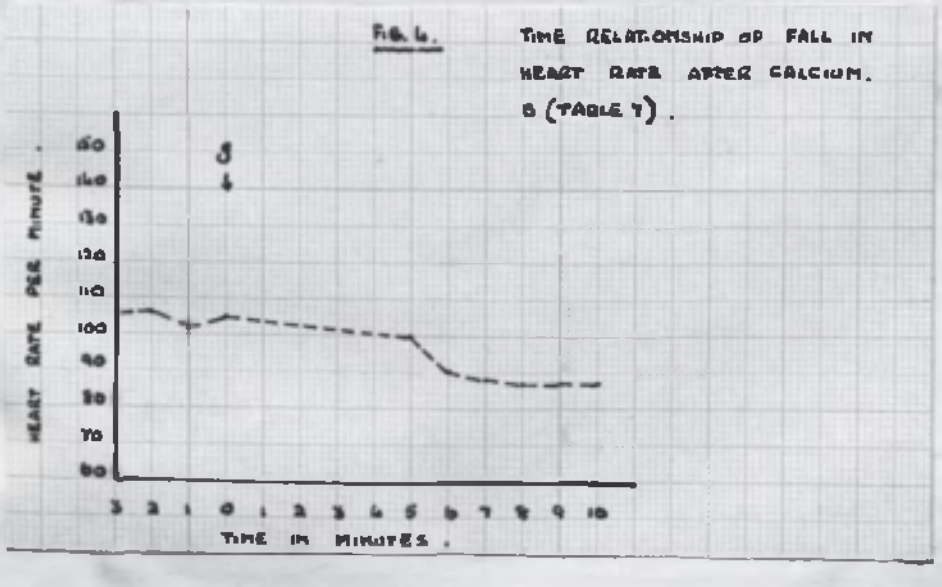



FIG. 4. TIME RELATIONSHIP OF FALL IN HEART RATE AFTER CALCIUM. 5 (TABLE 7).

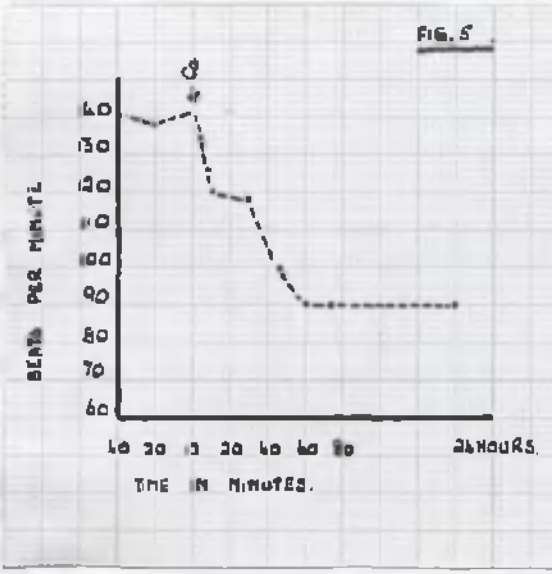



FIG. 5. TIME RELATIONSHIP OF FALL IN HEART-RATE AFTER ADMINISTRATION OF CALCIUM.
M (TABLE 7).

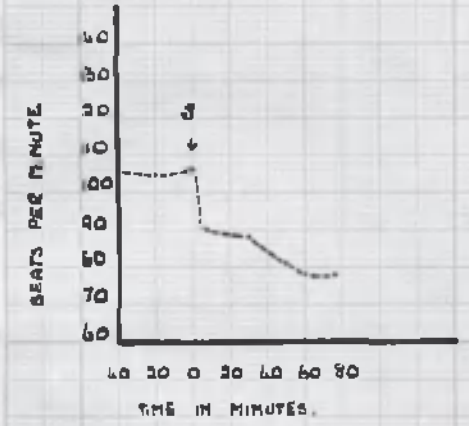



FIG. 6. TIME RELATIONSHIPS OF FALL IN HEART-RATE AFTER ADMINISTRATION OF CALCIUM.
M (TABLE 7).

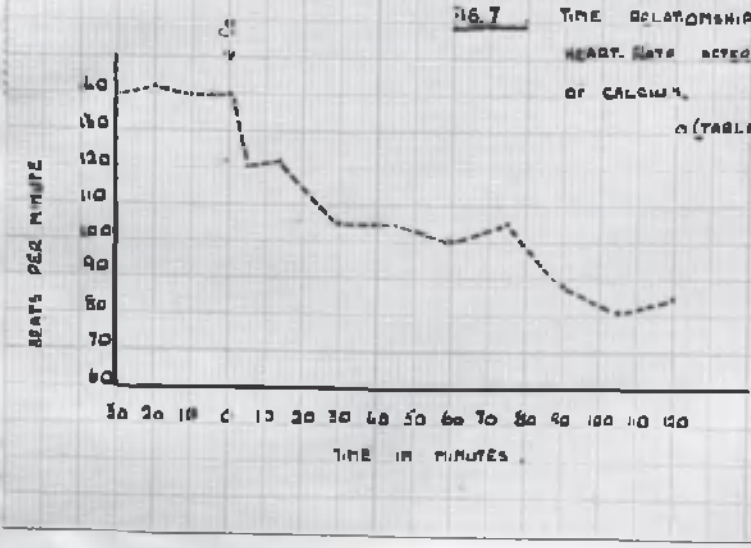



FIG. 7. TIME RELATIONSHIPS OF FALL IN HEART-RATE AFTER ADMINISTRATION OF CALCIUM.
O (TABLE 7).

An analysis of the results reveals the interesting fact that regularity of the heart rhythm plays an important part in determining the reaction of the heart beat to the administration of calcium. In five of the six cases in which there was no appreciable change in the heart rate the rhythm was irregular.

The maximum fall in patients with regular rhythm varied from twelve to seventy-eight with a mean of thirty-one. In patients with irregular rhythm the corresponding figures were six to twenty-eight with a mean of fourteen. Since the numbers of cases in the two groups were necessarily small, Fisher's 't' test was made use of to determine the statistical significance of these results. It was found that P was approximately 0.01, i.e., the odds are 100 to 1 that the difference between the two groups is not a chance one. Similar results are obtained when the fall in heart rate is estimated as a percentage of the original. In the patients with regular rhythm there was a tendency for a longer interval to elapse before the reduction reached a maximal figure. Thus, in half of the cases with regular rhythm the greatest degree of slowing did not occur within ten minutes of the intravenous injection of calcium, whereas in all the patients with irregular rhythm the maximal fall appeared within ten

minutes.

It seems natural to expect that the actual fall in heart rate produced by calcium would depend on the original rate. This proved to be true only when the rhythm was regular. Figure 8 illustrates the relationship between the percentage fall and the original heart rate and shows that they are roughly proportional to one another. In patients with irregular rhythm no such relationship could be established between the original heart rate and the percentage slowing.

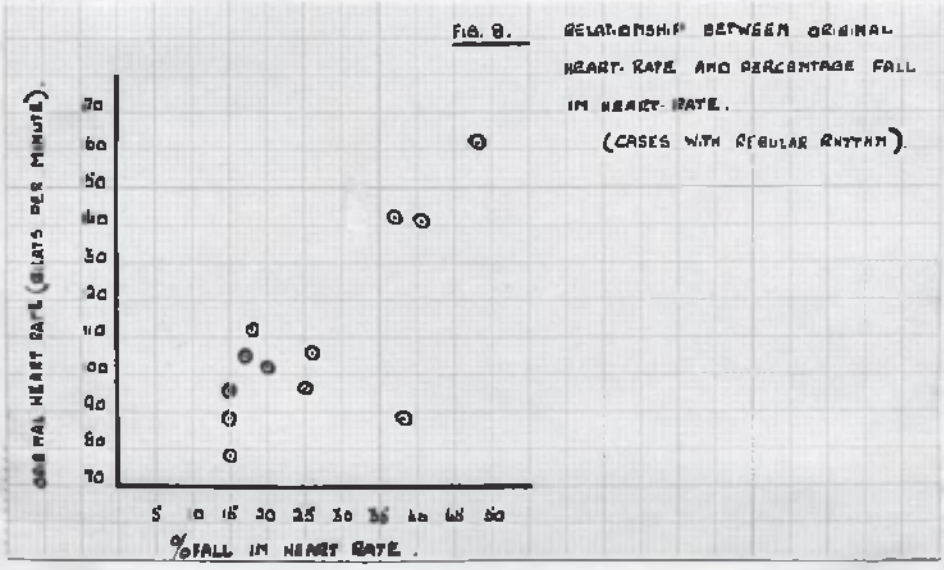



FIG. 8. RELATIONSHIP BETWEEN ORIGINAL HEART-RATE AND PERCENTAGE FALL IN HEART-RATE. (CASES WITH REGULAR RHYTHM).

These findings would appear to throw some light on the locus of action of calcium. In patients with regular rhythm all the heart beats arise from the normal pace-maker, the sino-auricular node which is under the control of the vagus mechanism. In patients with

irregular rhythm many of the beats are ectopic in origin and therefore not controlled by the vagus. The relationship between percentage fall and original rate in patients with regular rhythm and the absence of this when there are beats of ectopic origin suggests that one action of calcium is to stimulate the vagus mechanism.

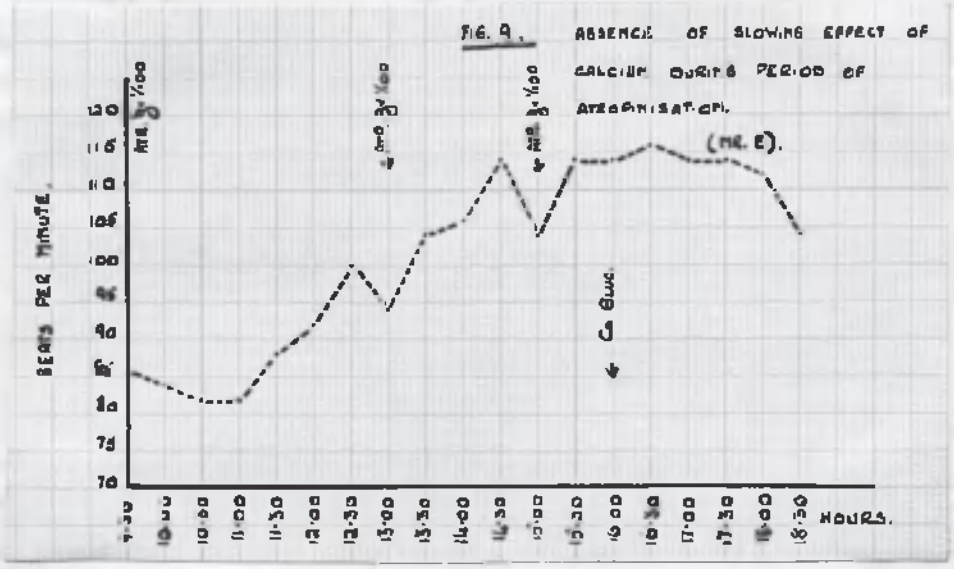
(e) The Mode of Action of Calcium on the Heart with Special Reference to (1) Atropinisation.

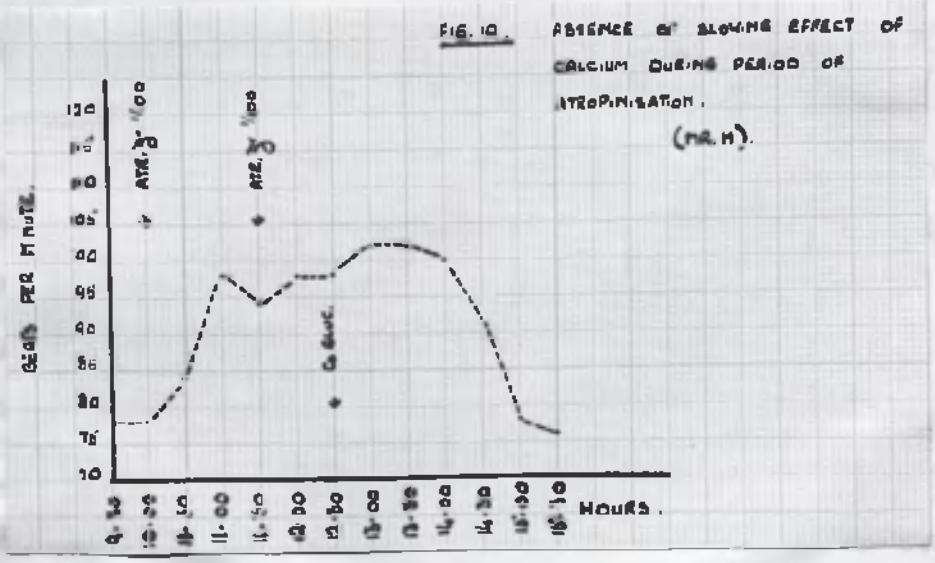
Previous work in this connection has already been reviewed. During the present study opportunity was taken to determine the effect of atropinisation on the action of calcium on the heart. The subjects of this part of the investigation were fifteen patients who had tachycardia associated with cardiac failure. In all cases the rhythm was regular. In each instance the slowing response to the calcium injection was demonstrated either two days before or some time after the test with atropine. Atropine sulphate was given in doses of gr.1/100 hypodermically twice or three times at short intervals. When the heart rate had risen to a maximum and remained fairly stationary for fifteen minutes 10 c.cs. of a 10% solution of calcium gluconate were given intravenously.

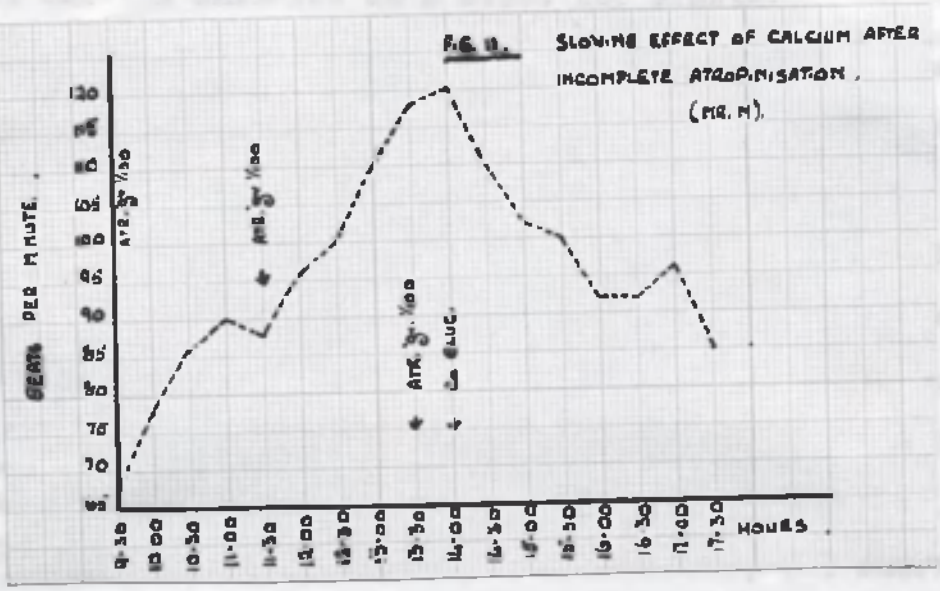
In ten of the fifteen patients calcium failed to have any effect on the heart rate during the period of atropinisation, but in the remaining five slowing resulted. The lack of slowing effect in these ten cases, in the presence of vagal paralysis, suggests that it is by stimulation of the vagus that the fall is normally brought about. The failure of atropine in the latter group to prevent the calcium effect on the heart rate might, I think, be reasonably attributed to a dosage of atropine which was insufficient to render the vagus nerve endings completely

insensitive to the action of calcium.

These results are shown in fifteen graphs. Two of the first group, Figs. 9 and 10, and one of the second, Fig. 11, are shown here as examples. The others are shown in appendix (c). The eventual drop in the rate in those ten showing lack of response to calcium is, of course, due to the effect of the atropine wearing off.






(e) contd. The Mode of Action of Calcium on the Heart with Special Reference to (2) The Electrocardiogram.

Kraus (28) was the first to use the electrocardiograph in the investigation of the action of calcium on the heart. In rabbits and guinea-pigs he observed the following changes in the tracings - deepening of the 'S' waves, slowing of the rate, disappearance of the 'P' waves, flattening of the 'T' waves and widening of the QRS interval. When calcium was administered to dogs until they died, ventricular tachycardia and ventricular fibrillation were noted. Berliner ( 2 ), writing in 1933, noted that up till that time only one human patient had been investigated in this manner and that was by Segall and White who gave 75 c.cs.

of 2% calcium chloride at 5 c.cs. per minute. Electrocardiograms taken before and five minutes after the injection showed no difference. Berliner, however, found effects on the tracing in the shape of increase of the 'P' waves and changes in the amplitude and direction of the 'T' waves. Segall and White (47), in 1935, took electrocardiograms from eleven patients receiving calcium salts by mouth. In eight they noted one or more of the following effects - slowing, variations in the length of the 'PR' interval, increase in the 'T' wave, and increase or decrease in the 'P' wave. Berliner ( 3 ), writing again in 1936, described more fully his work in this field. He gave 10 c.cs. of 20% calcium gluconate in a period of fifteen seconds to twenty-six normal people. The 20% solution had to be given in not more than fifteen seconds in order to produce the changes in the electrocardiograms. The principal effects of calcium on his twenty-six cases were found by Berliner to be :-

(1) Bradycardia in seventeen.

(2) Changes in the 'P' waves in fourteen.

(3) Changes in the 'T' waves in twenty-four.

(4) Ventricular premature beats.

(5) Sinus arrhythmia: where this was present before, the injection markedly intensified it.

(6) In two cases there was sinus arrest, both temporary and without subsequent ill effects.

It was concluded that calcium has a direct effect on the myocardium as shown by the changes in the 'P' and 'T' waves. That this effect is immediate was indicated by the changes in the 'T' wave occurring within four seconds of the end of the injection.

In the present investigation the effect of the intravenous administration of 10 c.cs. of 10% calcium gluconate on the electrocardiogram was studied in twelve patients. Tracings were taken immediately prior to the intravenous injection, in some cases during the injection, and between two and fifteen minutes after the injection was completed. They are numbered from 2 to 13; tracings 1 are shown in Part IV. A short explanatory note accompanies each set of tracings.

The view that one effect of calcium is to stimulate the vagus mechanism is supported by evidence which has already been adduced in the course of this investigation. The electrocardiograms lend further support to this view. The records show that in all cases there is definite indication of slowing due to some action on the pace-maker and therefore on the vagus. Furthermore, the fact that calcium is particularly effective in slowing the heart rate when the rhythm is regular, and that bradycardia is not so commonly obtained when there is gross irregularity also

supports this view. Only the impulses arising from the sino-auricular node would be affected since these are controlled by the vagus. The ectopic beats, not being influenced by vagal action, would not be reduced in number by the vagal action of calcium.

The evidence as to the direct action of calcium on the cardiac musculature has been obtained chiefly from experimental work on animals. Little is available in this connection from the investigation on patients with cardiac failure. It is possible that any strengthening of the heart beat may be due to cutting down the frequency and thus allowing more time for diastole, a better recovery from fatigue, and a more efficient coronary circulation. Nevertheless it is worth mentioning that in two cases (Tracings 11 and 12) changes in the records indicate improvement in the action of the myocardium immediately after the injection of calcium. In the former, increase in amplitude of the QRS complex was noted, and in the latter increase in the amplitude of 'T'. These findings suggest a direct action of the calcium on the heart muscle. The change in the type of 'T' wave, as shown in tracings 13, from a diphasic to a shouldered to a normal 'T', was thought to indicate an improvement in the coronary circulation. Berliner mentions the possibility of calcium having an action on the coronary arteries. But it would appear that the change in the appearance of the wave is due

rather to the slowing up of the rate, so that the 'P' and preceding 'T' waves become superimposed.

The decrease in the number of supraventricular extrasystoles, shown in tracings 7, suggests an effect on the intrinsic excitatory mechanism which seems to be inhibited.

The tendency to coupling obtained in the tracings from case 12 afford evidence of some similarity in the action of calcium and digitalis.

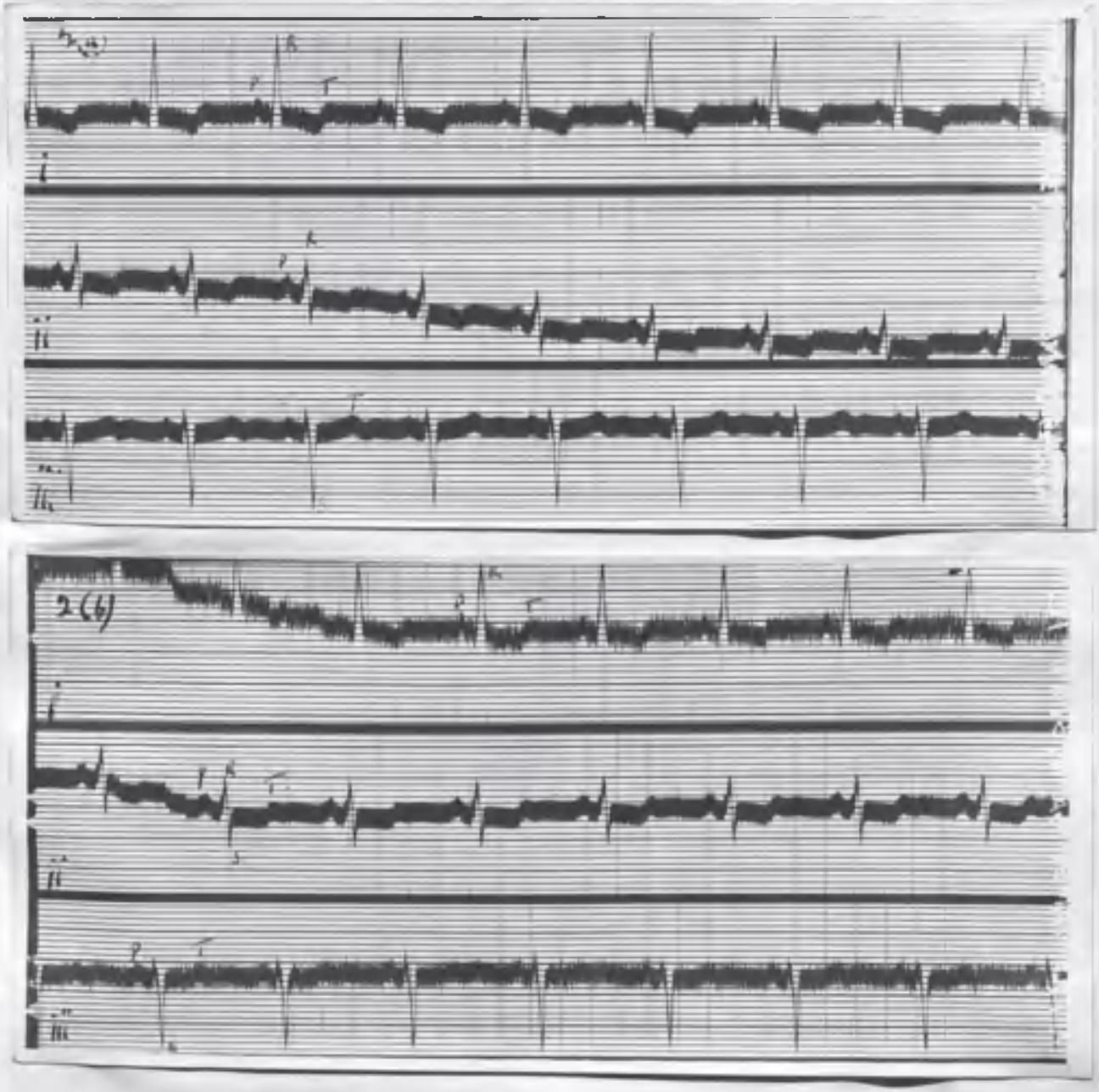
A survey of the findings obtained from the tracings indicates that in the dose and rate of administration used, calcium gluconate does not produce toxic effects but, on the contrary, leads to changes such as slowing of the heart rate, improvement in the action of the myocardium and abolition of extrasystoles which are of benefit to the patient with cardiac decompensation.

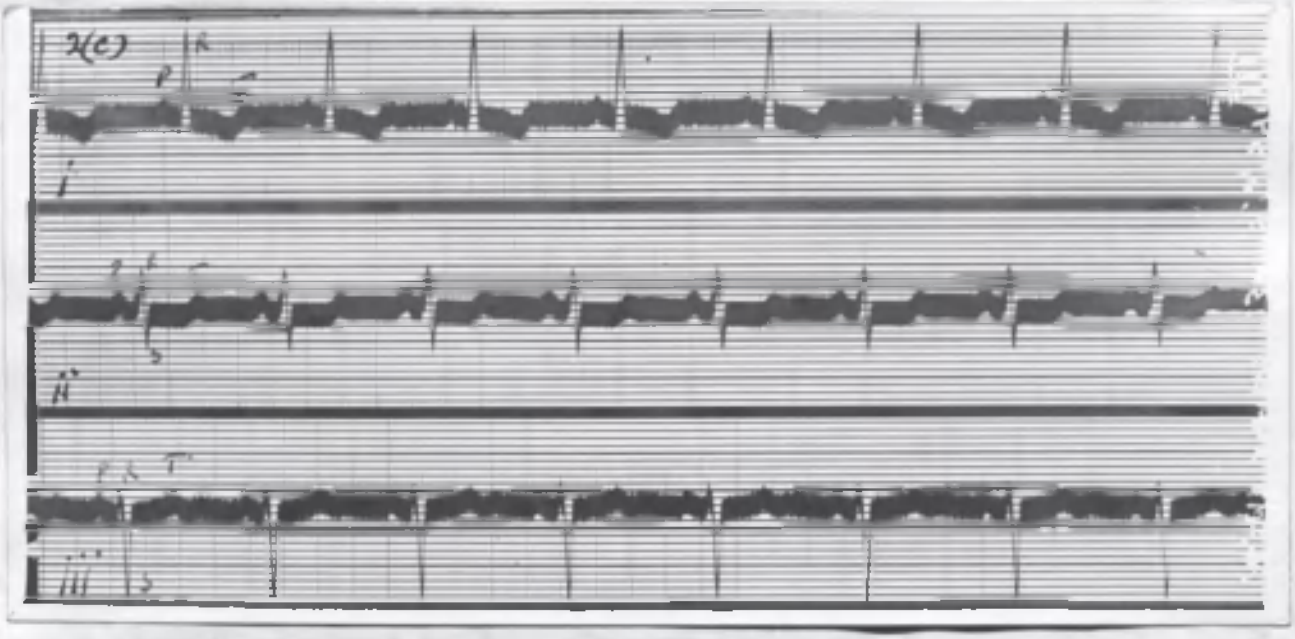
Case 2.

Tracings were taken before, 2 (a), during, 2 (b), and five minutes after the termination of the calcium injection, 2 (c).

---

Sinus slowing of the rate is shown.




2(c)
i
ii
iii

Case 3.

(a) ... Before injection.

(b) ... During injection.

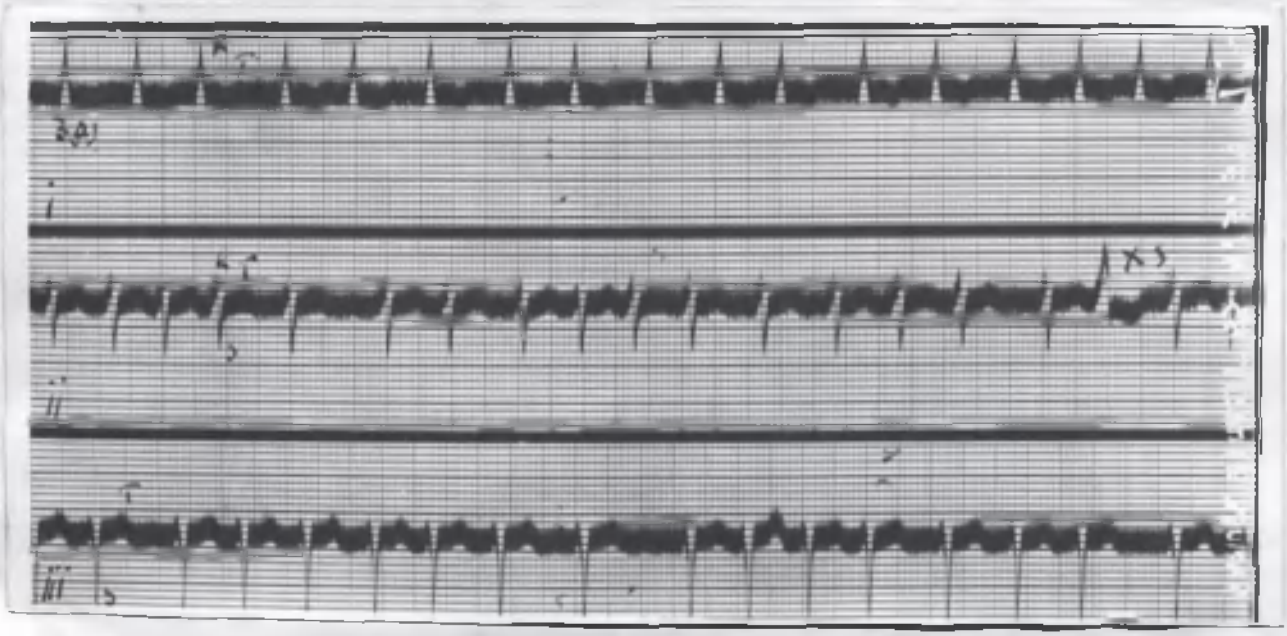
(c) ... Five minutes after injection.

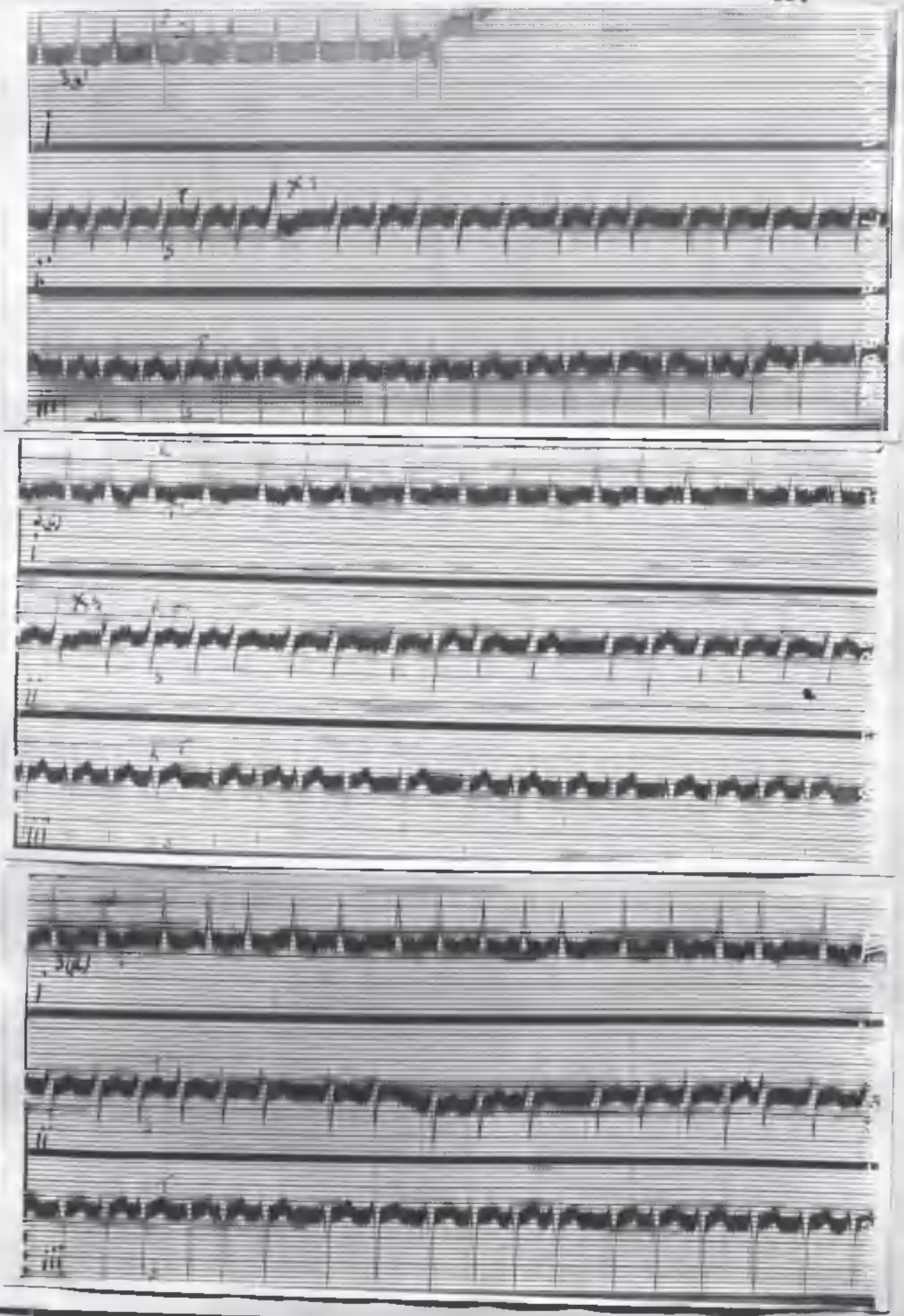
(d) ... Ten minutes after injection.

---

Sinus slowing of rate (there was a slight acceleration during the actual injection).

Sinus arrhythmia intensified.





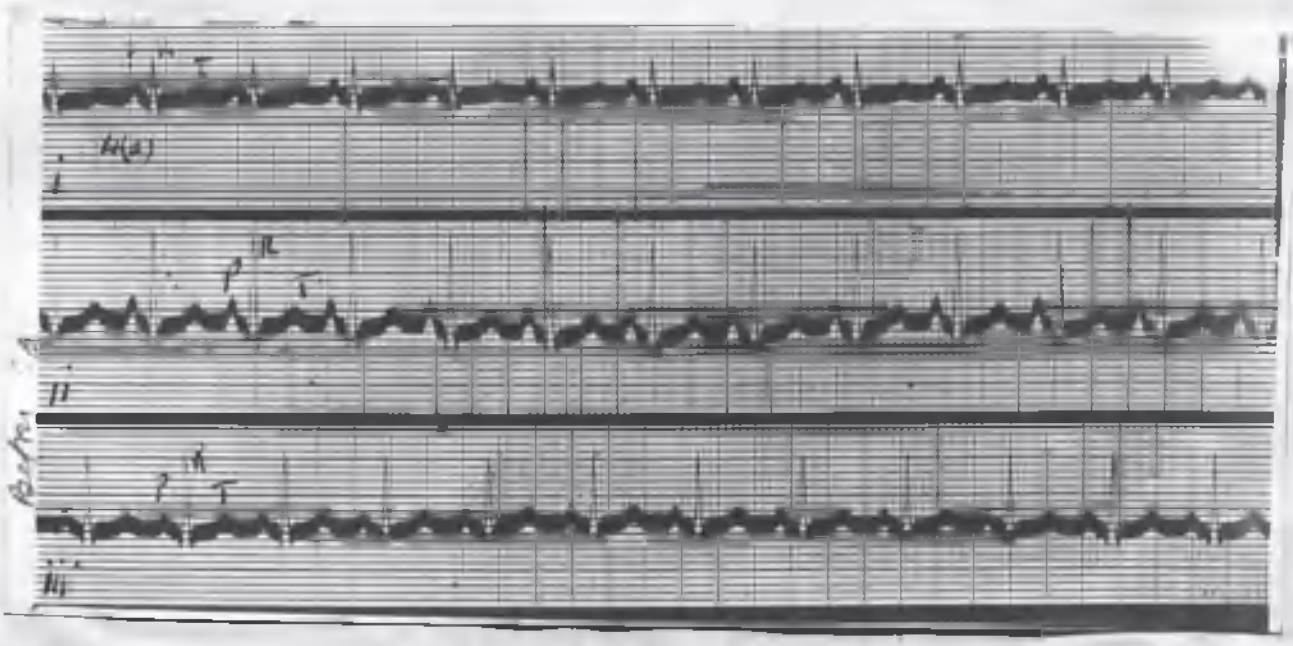
Case 4.

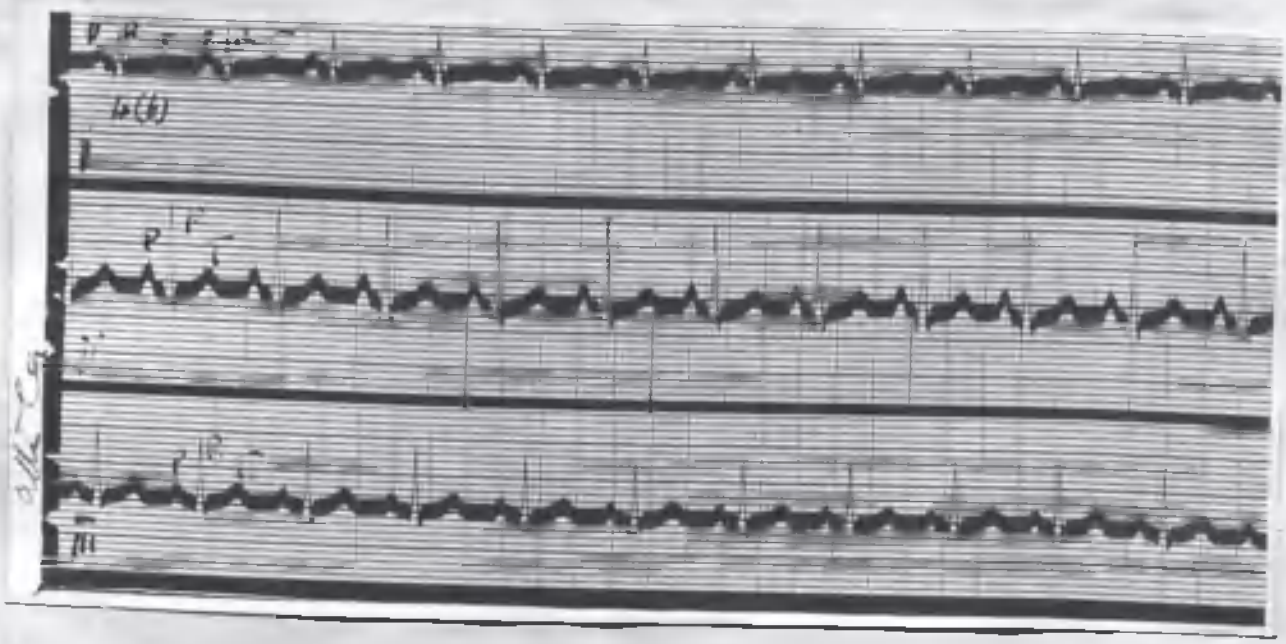
(a) ... Before calcium.

(b) ... Five minutes after calcium.

---

Sinus slowing of rate.





Case 5.

(a) ... Before calcium.

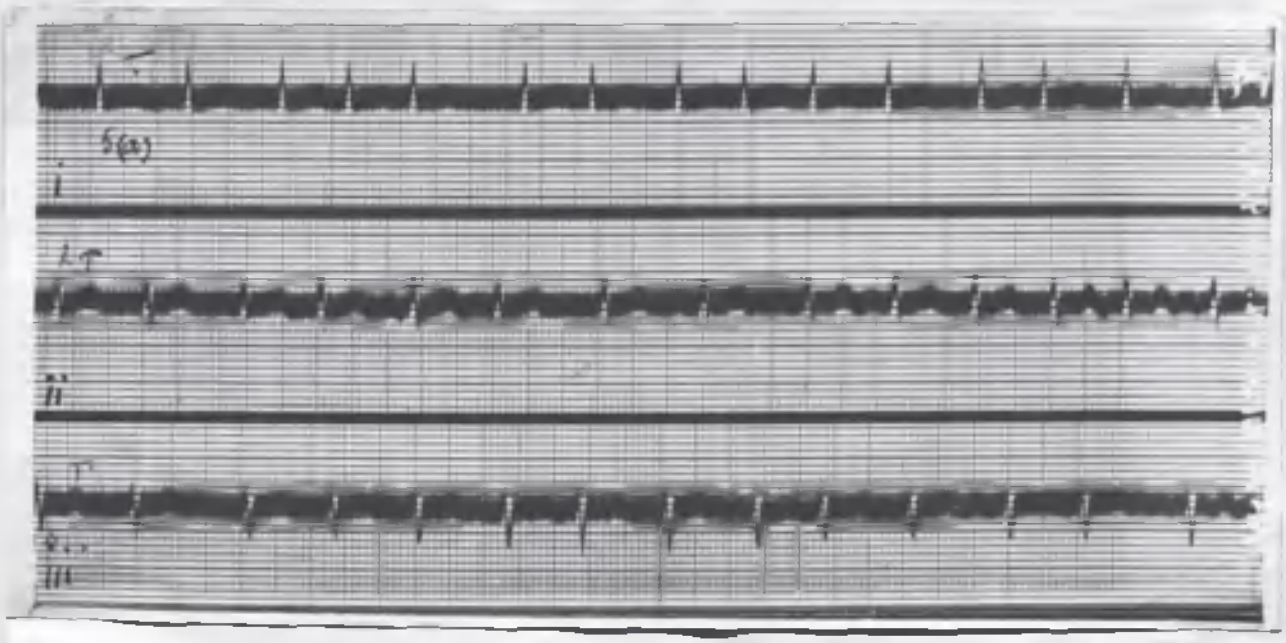
(b) ... During calcium.

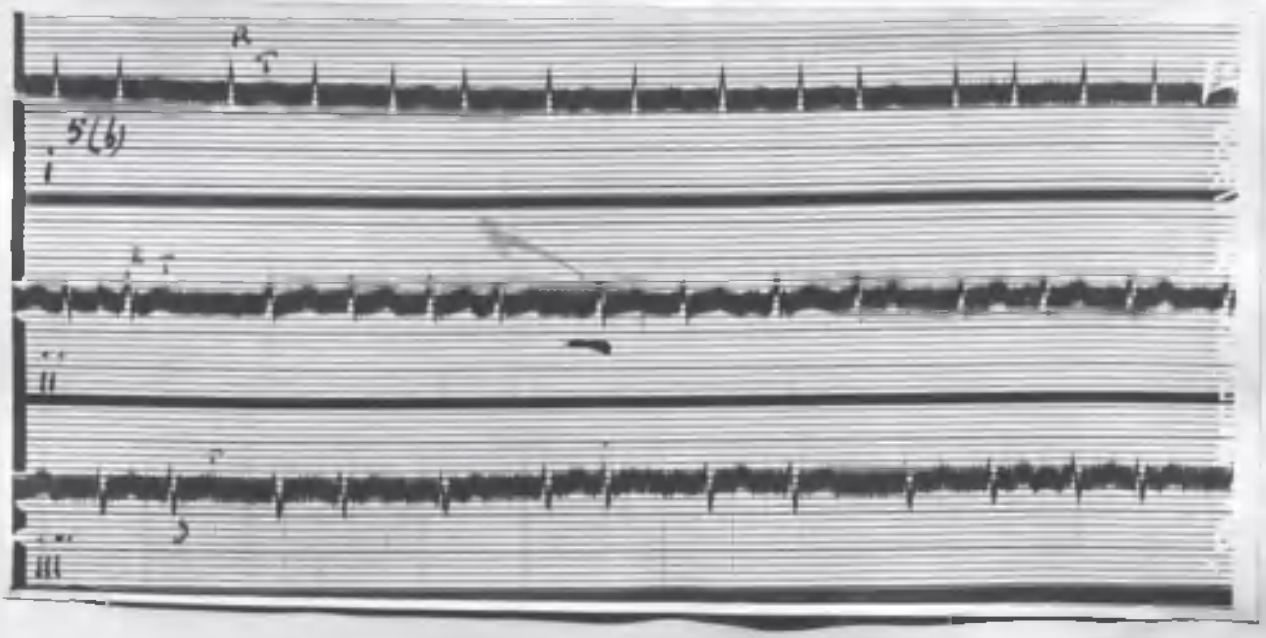
(c) ... Ten minutes after calcium.

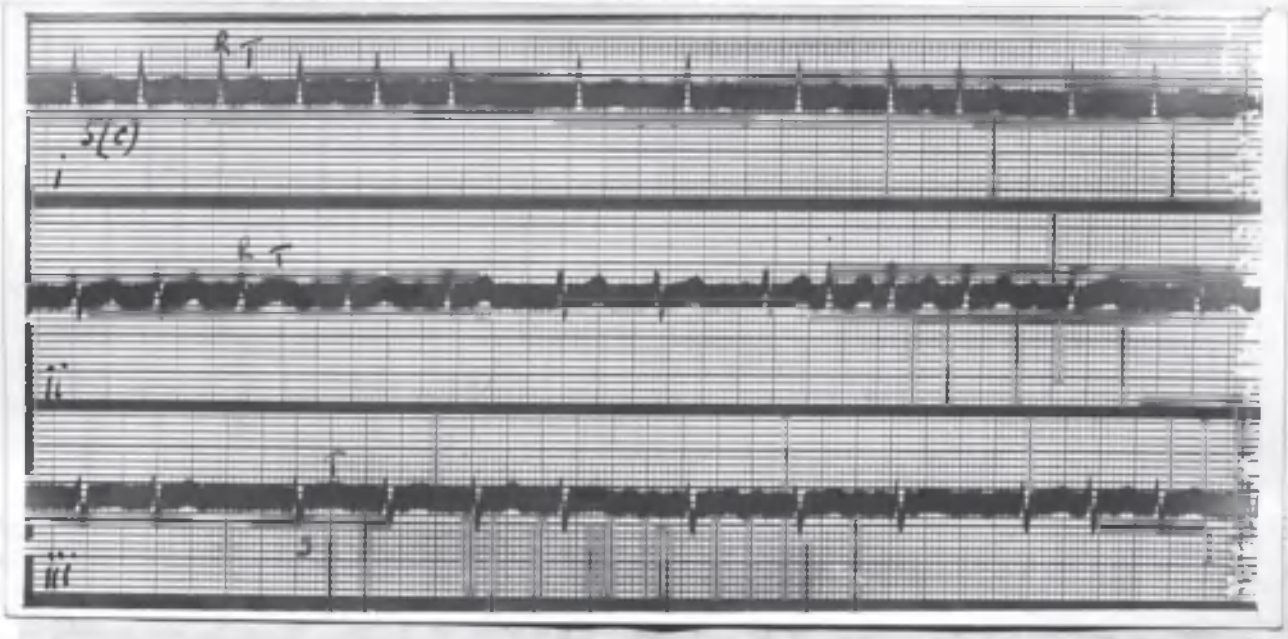
---

Sinus slowing of rate.

Sinus arrhythmia more marked.




R T
S(t)
i
R T
ii
iii

Case 6.

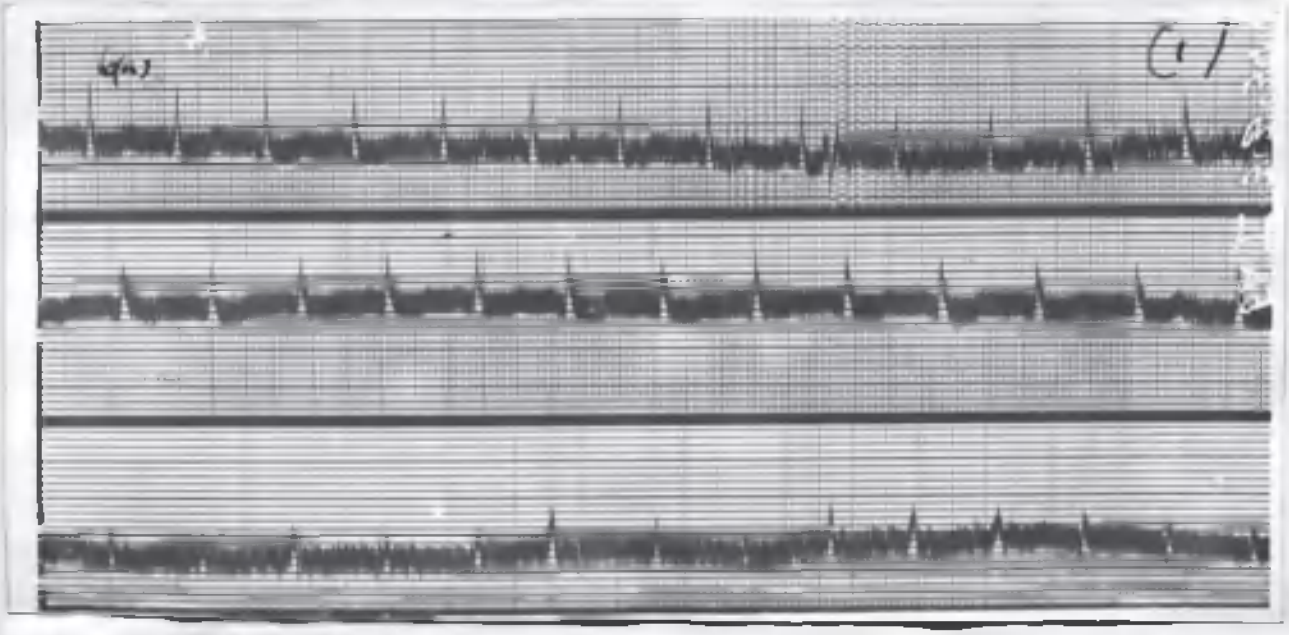
(a) ... Before calcium.

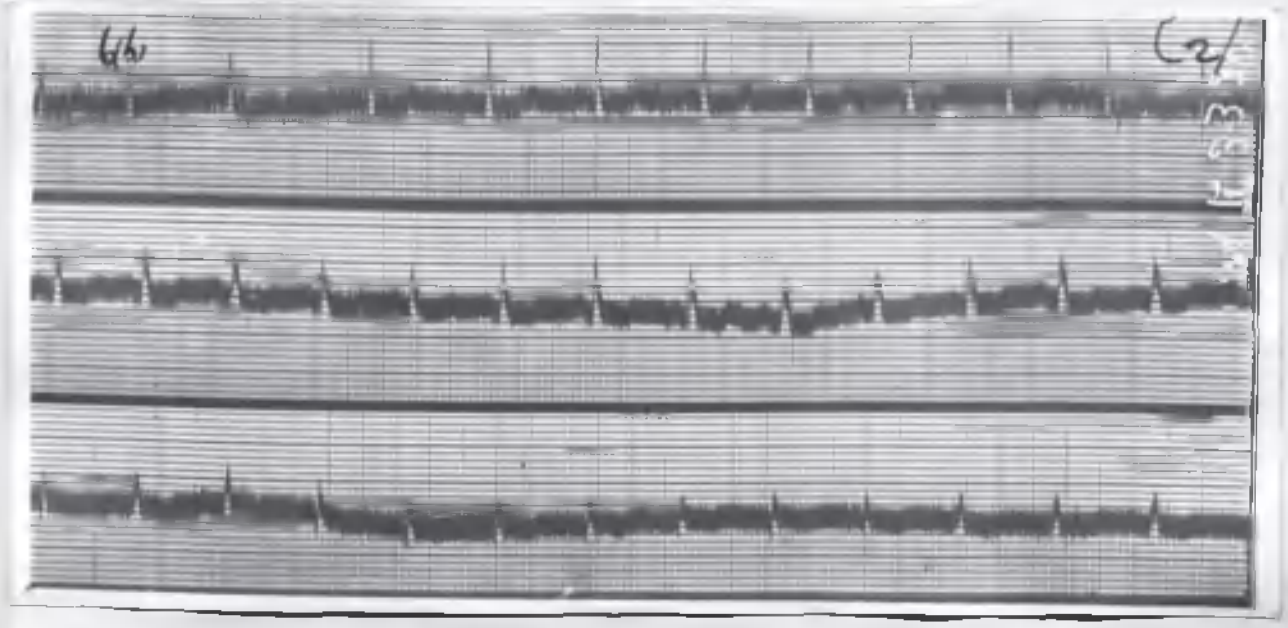
(b) ... During calcium.

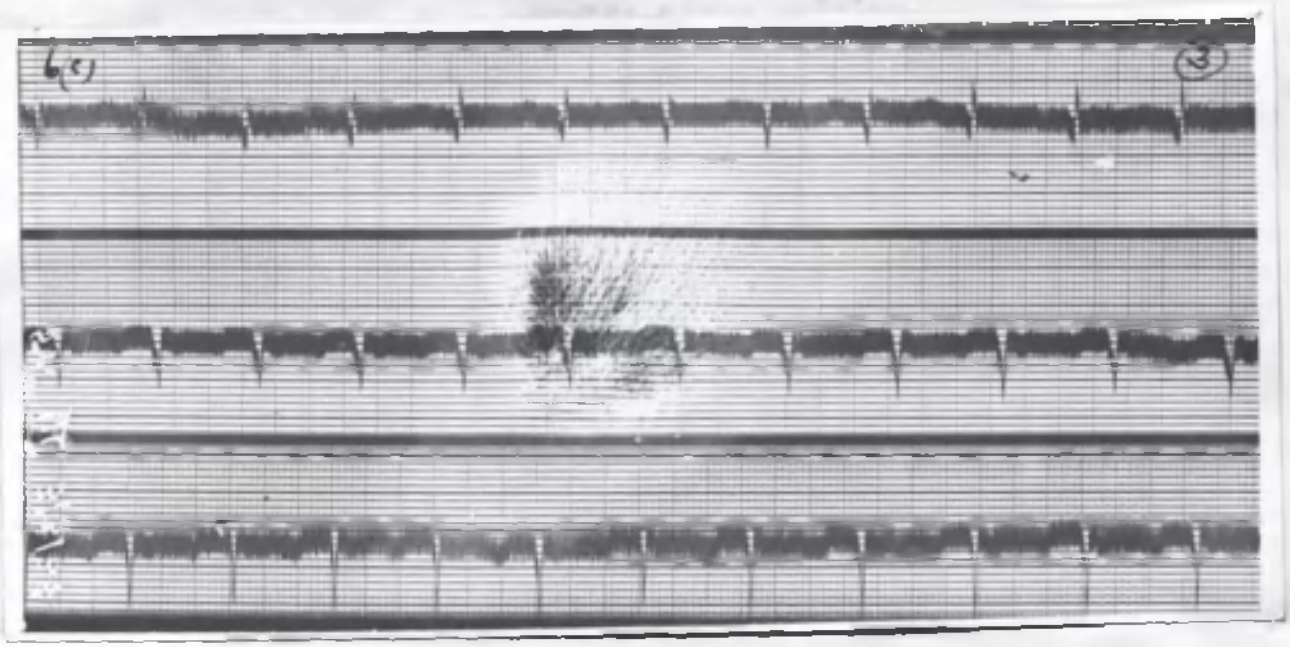
(c) ... Ten minutes after calcium.

---

Lengthening of diastole.




6(c)
3

Case 7.

(a) ... Before calcium.

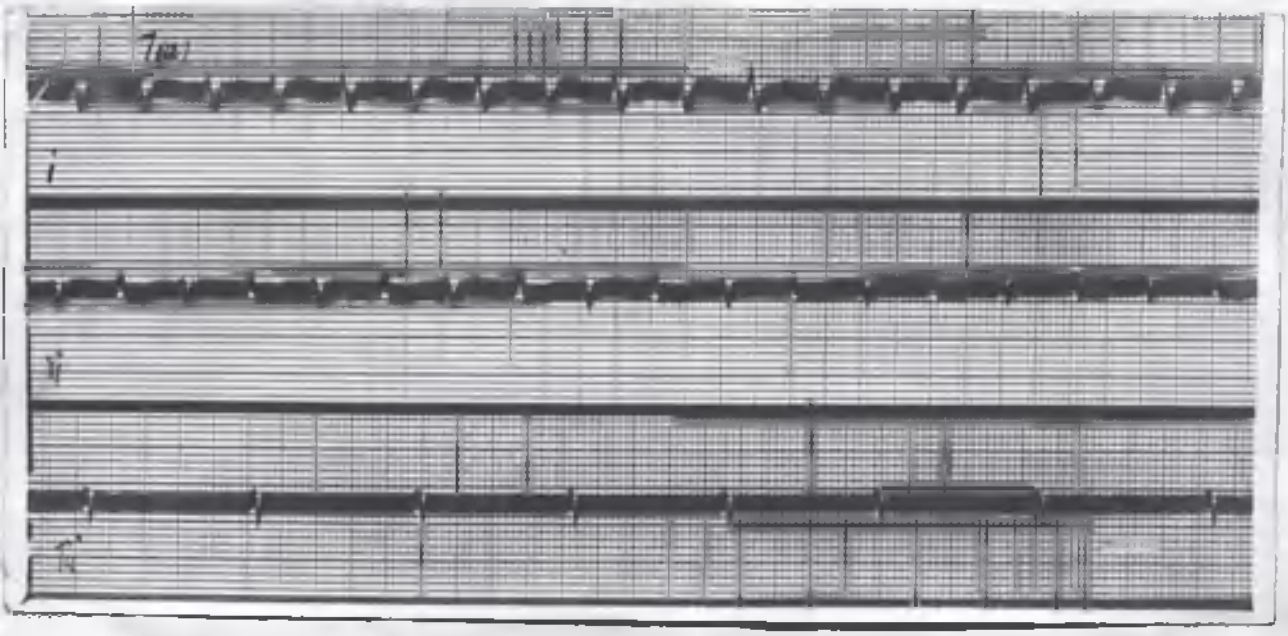
(b) ... Five minutes after calcium.

---

Supraventricular extrasystoles became less frequent. Whereas previously they occurred regularly, after calcium they became irregular.

(a) : In leads (1) and (2) a phase of tachycardia is present with a regular rhythm but alternate beats appear to be from two separate points of origin. In lead (3) the rate is half that in leads (1) and (2), and the control appears to be a normal sinus rhythm.

(b) : Shows irregularly recurring extrasystoles, supraventricular in origin and the abnormality in the original tracing was considered due to regularly recurring extrasystoles.


i
ii
iii


i
ii
iii

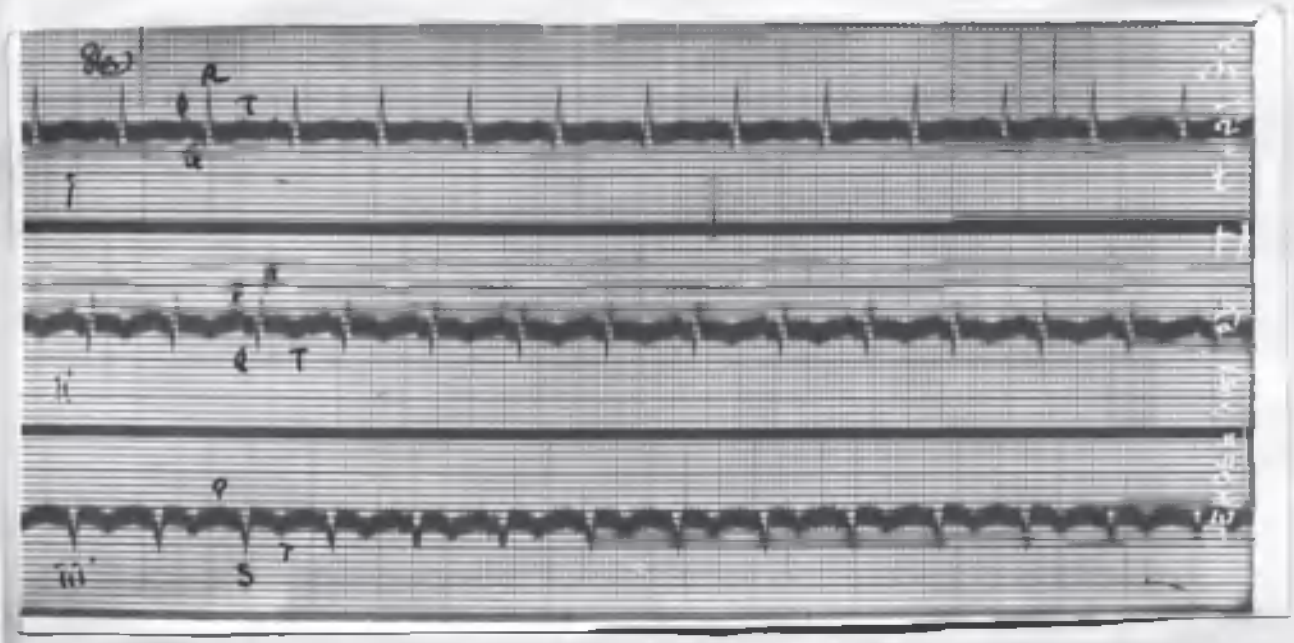
Case 8.

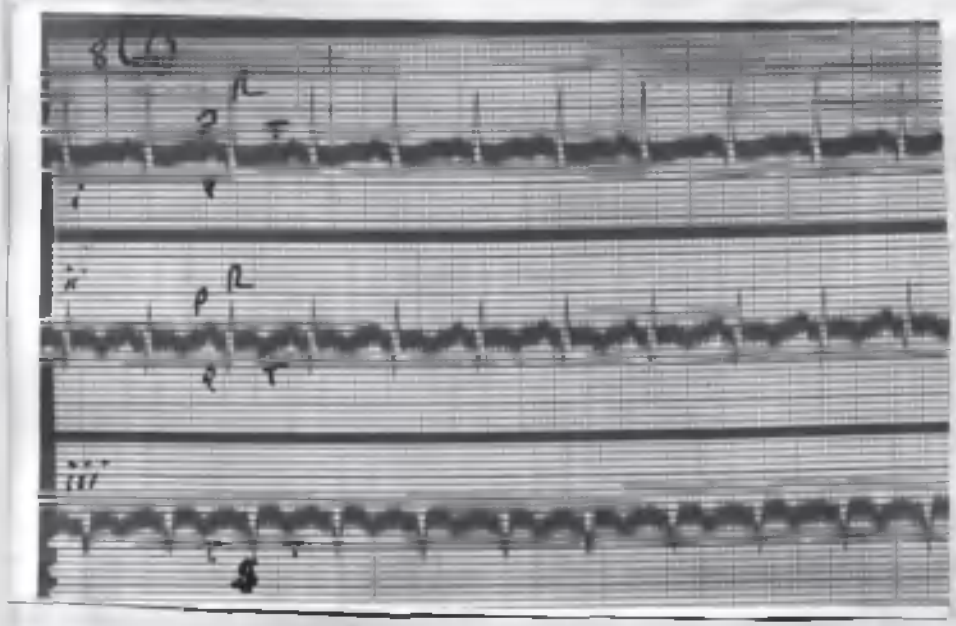
(a) ... Before calcium.

(b) ... Fifteen minutes after calcium.

---

No significant difference.





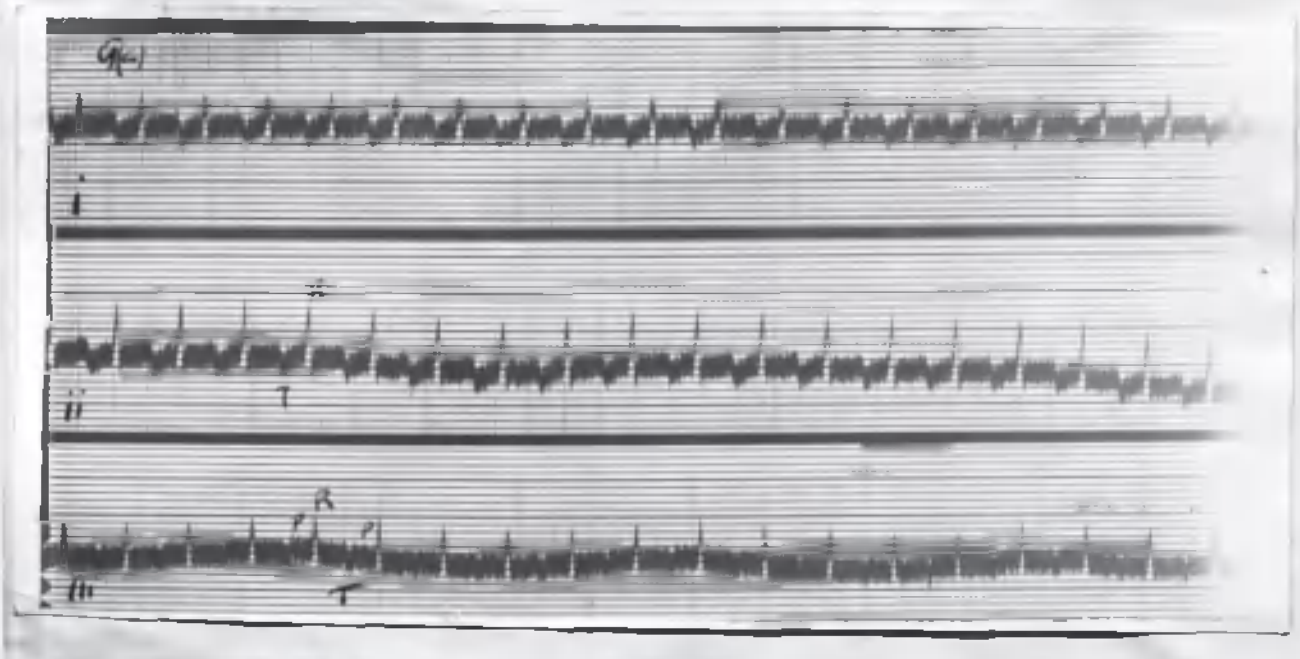
Case 9.

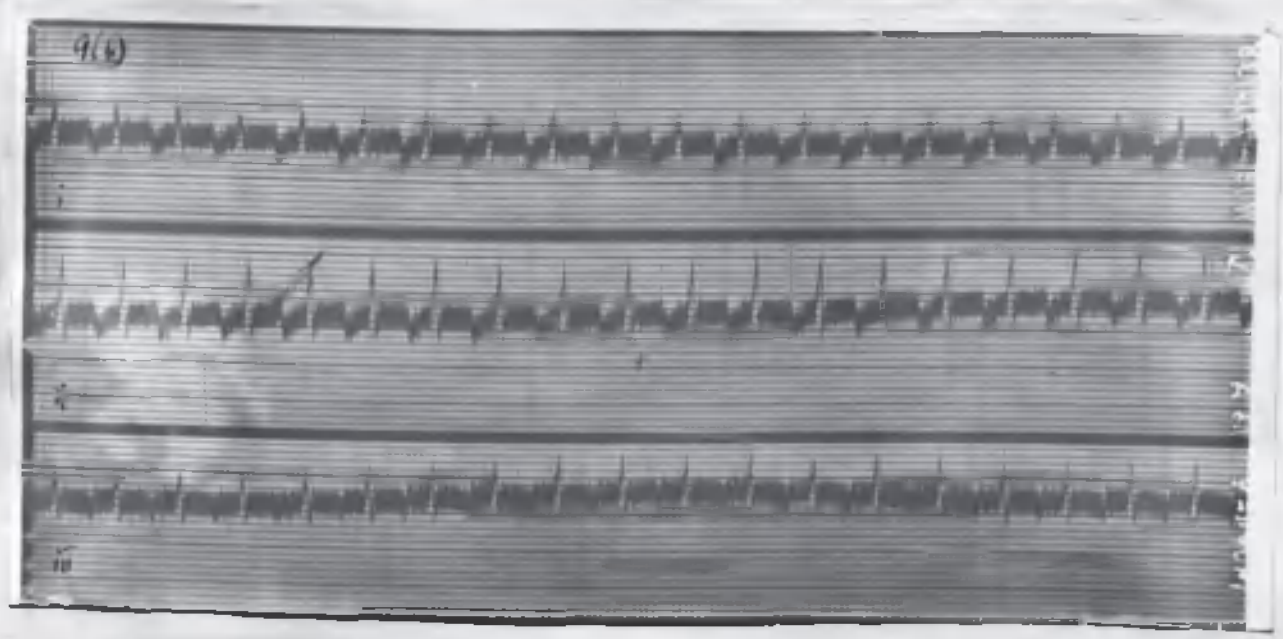
(a) ... Before calcium.

(b) ... Five minutes after calcium.

---

Slight lengthening of diastole.



Case 10.

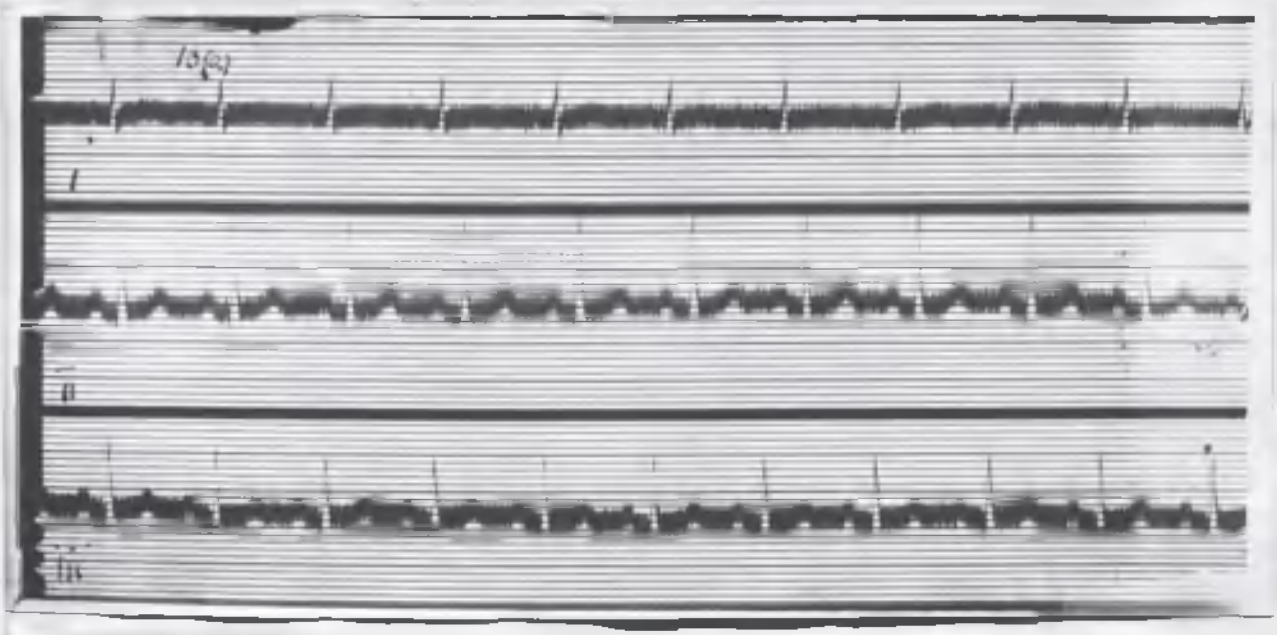
(a) ... Before calcium.

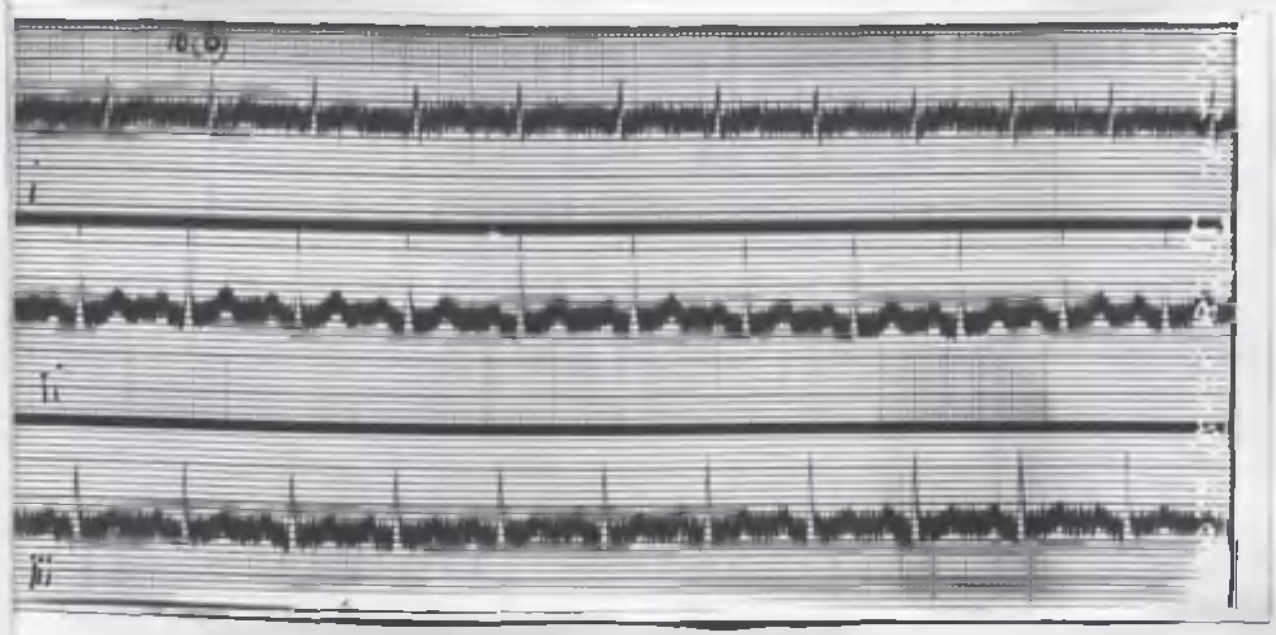
(b) ... During calcium.

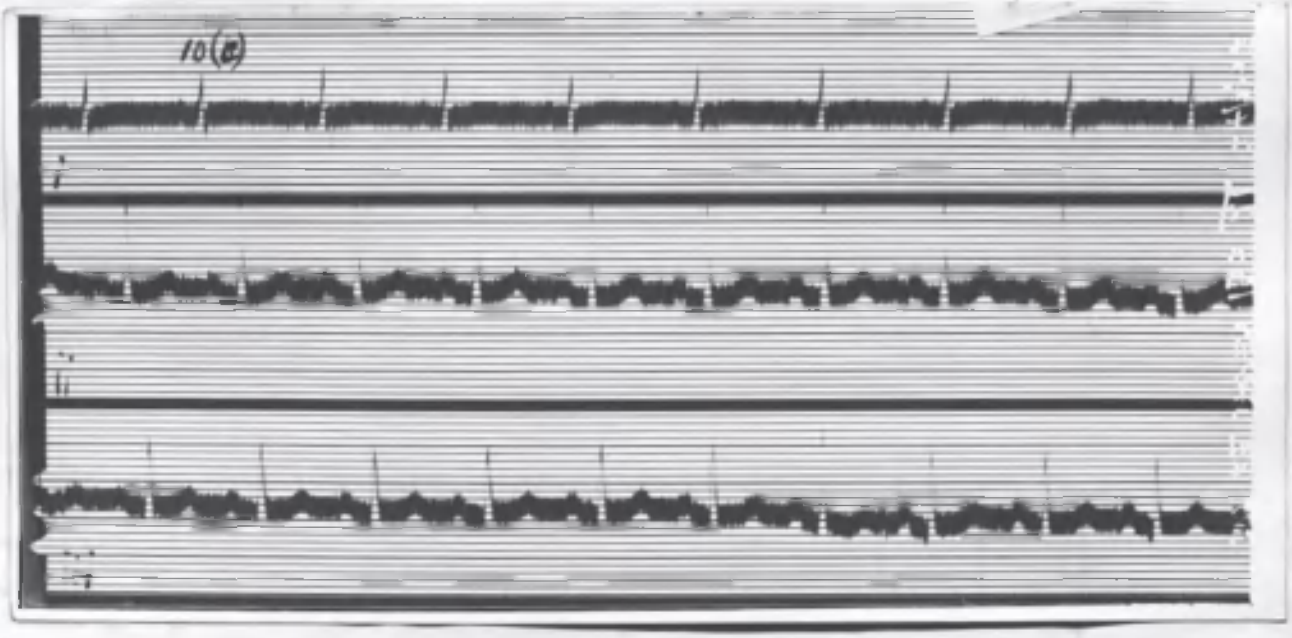
(c) ... Ten minutes after calcium.

---

Sinus slowing of rate.




10(a)

Case 11.

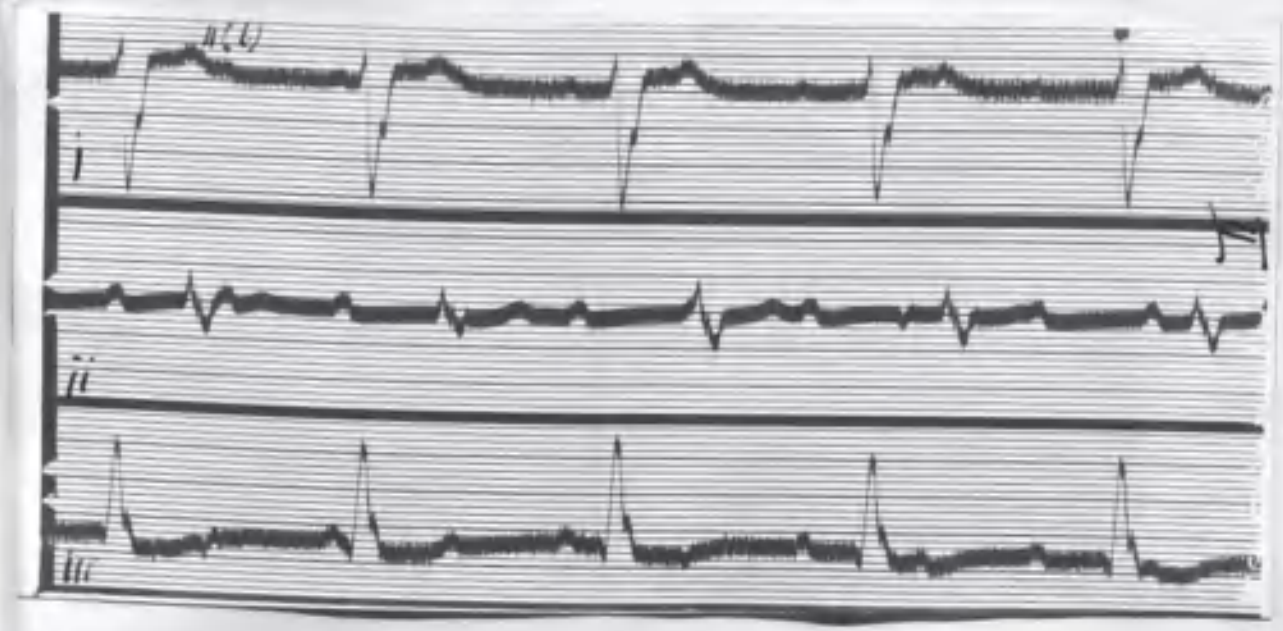
(a) ... Before calcium.

(b) ... Five minutes after calcium.

---

Full heart block.

Sinus slowing of rate and increased voltage in ventricular deflections.

Case 12.

(a) ... Before calcium.

(b) ... During calcium.

(c) ... Immediately after calcium.

(d) ... Ten minutes after calcium.

---

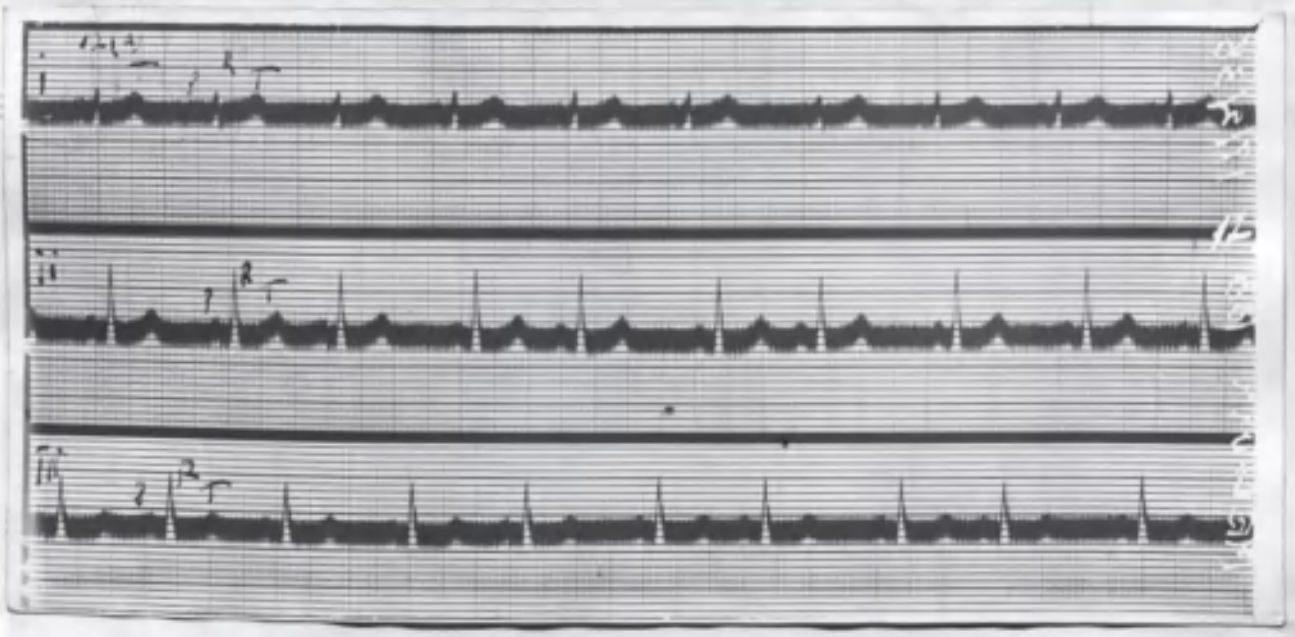
Sinus arrhythmia intensified.

Tendency to coupling increased (12 c).

Sinus slowing of rate.

R.T. interval increased from 0.11 to 0.14 (12 d)

Amplitude of 'T' increased by 1/10th mV.




II(b)
II(c)
I2(d)

Case 13.

(a) ... Before calcium.

(b) ... During calcium.

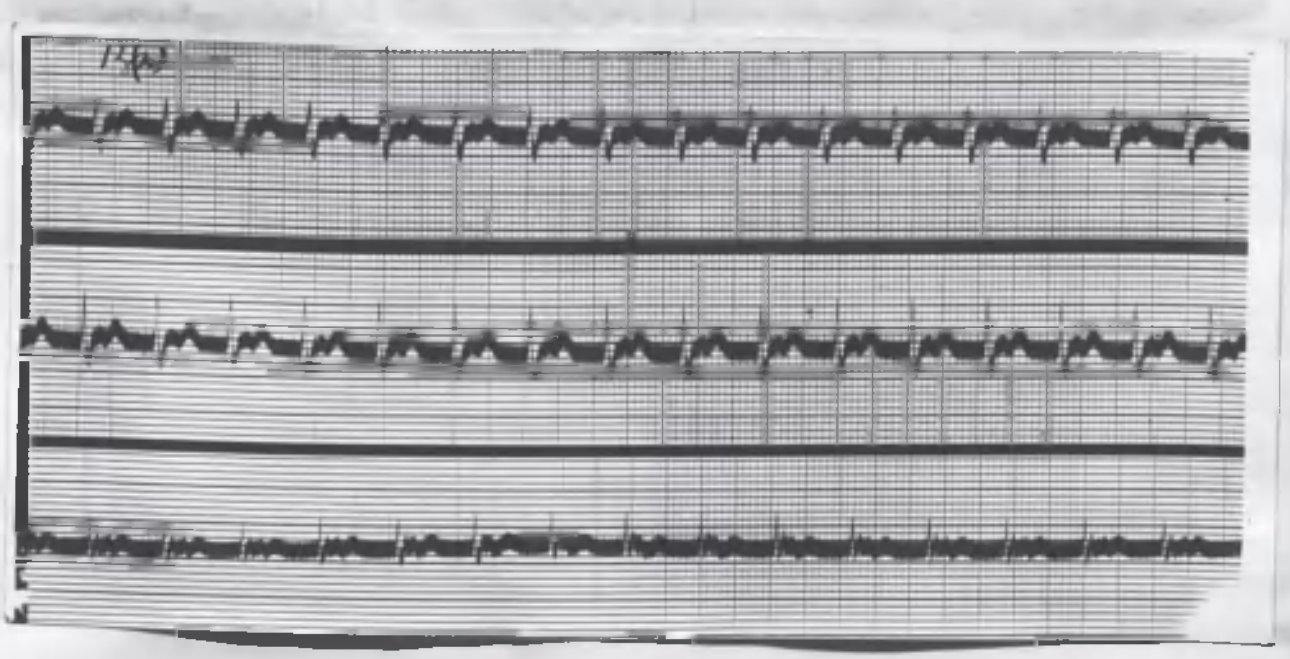
(c) ... Five minutes after calcium.

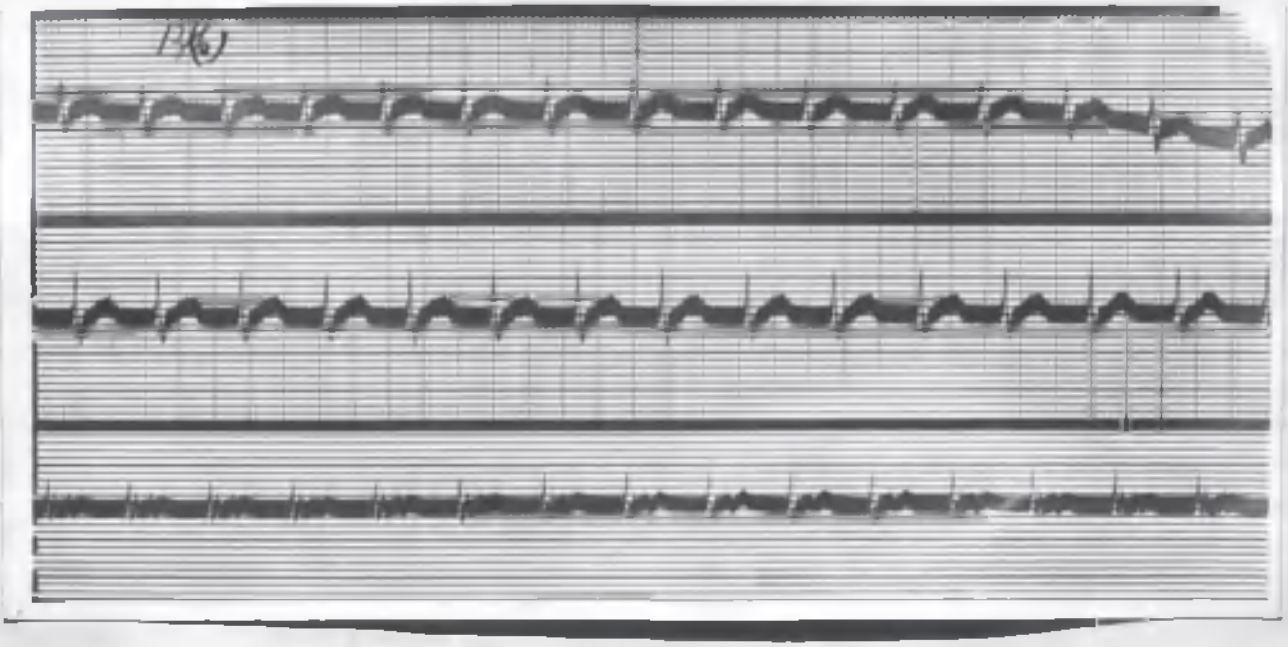
---

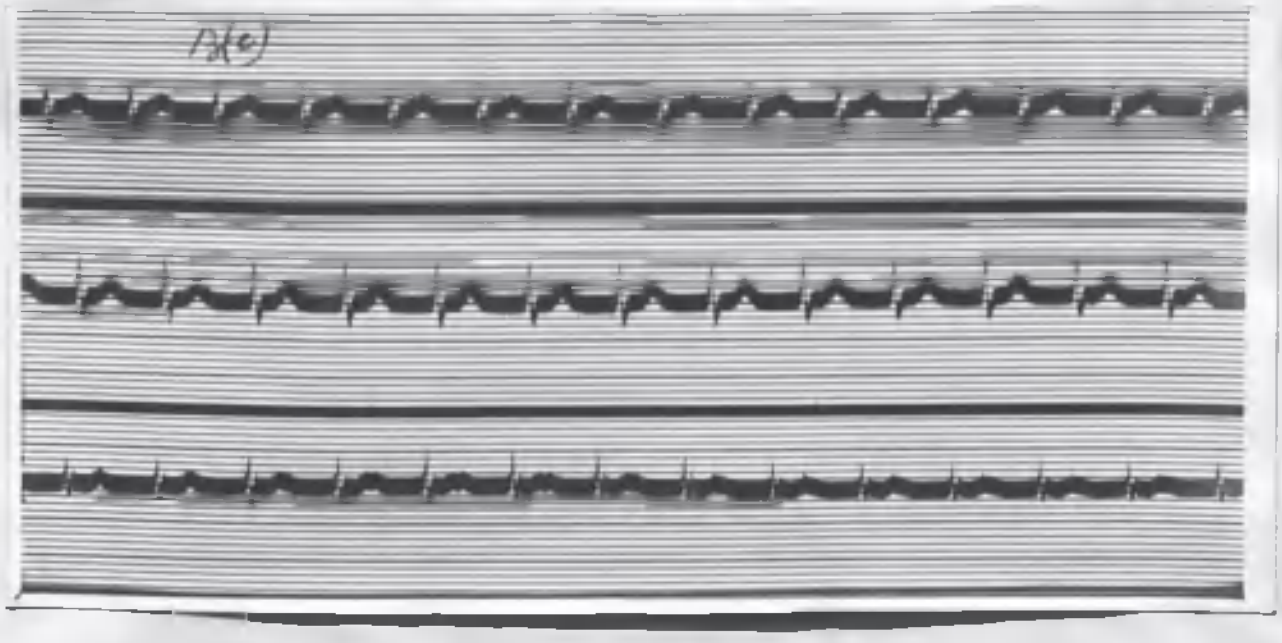
Sinus slowing of rate.

Alteration in type of T - P complex.

This was at first thought to be a progressive change in the 'T' wave - from diphasic to shouldered and then normal - possibly indicating some improvement in the coronary circulation. Further study, however, leads one to believe that the change is due rather to a sinus slowing of the rate so that the 'P' waves have become superimposed on the 'T' waves.




P1(b)


P1(c)

(e) contd. The Mode of Action of Calcium on the Heart with Special Reference to (3) Irregularities of the Pulse.

This is described at this place since most of the effects to be described may be seen in the electrocardiogram tracings.

(1) Sinus arrhythmia.

A tendency to this may be produced by the injection of calcium, and when it is already present, it may be increased. This may be seen in tracings 3, 5, 12.

(2) Tachycardia.

A rapid heart rate may be reduced by (a) lengthening of diastole or (b) a sinus slowing of the rate. This slowing effect, particularly noticeable when the rhythm is regular, has been stressed earlier.

(3) Supraventricular extrasystoles.

These may be made less numerous (tracings 7).

(4) Heart block.

No change was produced in the block in the one patient investigated. As seen in electrocardiogram tracings 11, the rate was still further slowed, and the ventricular deflections increased.

(5) Auricular fibrillation.

As a rule no permanent change is produced. In this condition, as in sinus tachycardia, there may be a slowing of the rate, but the irregularity persists. The only exception to this in the series examined was in the case of Mr. L. where auricular fibrillation of a marked degree was replaced after a series of calcium injections by extrasystoles recurring regularly after every fifth beat (electrocardiogram tracings 1 - Part IV).

In so far as this case had proved intractable to digitalis, it might be of service to try intravenous calcium in those cases where the fibrillation cannot be controlled by digitalis.

(6) Paroxysmal tachycardia.

Calcium was given to one patient during the acute attack. This patient, a woman of fifty-four, had severe praecordial pain and a heart rate of 116 per minute. Pain disappeared half way through the injection, the heart rate fell to 96 in five minutes, 88 in ten minutes, and remained at this level. Such a beneficial effect did not result, in a subsequent attack, from an injection of sterile water.

(7) Bundle-Branch block.

One patient who had right bundle-branch block had daily injections of 10 c.cs. of 10% calcium gluconate for twelve successive days. No change was noted in the electrocardiograms taken before and after the course of injections.

(f) Effect of Calcium on the Blood Pressure.

The survey of the previous work contained in Part 1 indicates a diversity of opinion as to the action of calcium on blood pressure. The present investigation yields varying results in different patients, and in the same patient on different days.

The blood pressure was determined in the usual way on the arm, half an hour before the injection was given, five minutes after the end of the injection, and in some cases later. No pressure was considered to be altered unless there was a greater difference than 4 millimetres of mercury from the original reading. Changes are classified as immediate or delayed according as they occurred within five minutes of the end of the injection or later. The results are given in detail in Table 9.

TABLE 9

Showing Changes in Blood Pressure (Systolic and Diastolic) and Pulse Pressure after Calcium Gluconate

| Name | Date | Systolic Pressure | | Diastolic Pressure | | Pulse Pressure | | Time at which Change Occurred. |
|---|---|---|---|---|---|---|---|---|
| | | Original | After Calcium | Original | After Calcium | Original | After Calcium | |
| A. | 6/6/38 | 140 | 122 | 70 | 60 | 70 | 62 | 5 mins. |
| | 7/6/38 | 148 | 146 | 74 | 68 | 74 | 78 | 5 mins. |
| | 8/6/38 | 126 | 146 | 80 | 90 | 46 | 56 | 3 hours |
| B. | 15/2/38 | 136 | 136 | 90 | 90 | 46 | 46 | 5 mins. |
| | 16/2/38 | 110 | 116 | 80 | 78 | 30 | 38 | 5 mins. |
| | 17/2/38 | 124 | 130 | 84 | 90 | 40 | 40 | 5 mins. |
| C. | 9/5/38 | 166 | 166 | 100 | 100 | 66 | 66 | 5 mins. |
| | 11/5/38 | 160 | 154 | 94 | 88 | 66 | 66 | 5 mins. |
| | 13/5/38 | 154 | 174 | 80 | 92 | 74 | 82 | 4 hours |
| | 14/5/38 | 160 | 154 | 90 | 80 | 70 | 74 | 5 mins. |
| | 16/5/38 | 158 | 168 | 100 | 98 | 58 | 70 | 3 hours |
| D. | 27/5/38 | 164 | 160 | 110 | 120 | 54 | 40 | 5 mins. |
| | 28/5/38 | 176 | 170 | 130 | 130 | 46 | 40 | 5 mins. |
| E. | 16/2/38 | 116 | 104 | 70 | 70 | 46 | 34 | 5 mins. |
| | 17/2/38 | 108 | 104 | 74 | 70 | 34 | 34 | 5 mins. |
| F. | 7/2/38 | 172 | 175 | 120 | 136 | 52 | 39 | 5 mins. |
| | 8/2/38 | 190 | - | 120 | - | 70 | - | - |
| | 9/2/38 | 170 | - | 118 | - | 52 | - | - |
| | 10/2/38 | 184 | 180 | 120 | 120 | 64 | 60 | 5 mins. |
| G. | 7/2/38 | 220 | 230 | 120 | 120 | 100 | 110 | 5 mins. |
| | 8/2/38 | 200 | - | 150 | - | 50 | - | - |
| | 9/2/38 | 204 | 225 | 130 | 144 | 74 | 81 | 5 mins. |
| H. | 12/3/38 | 110 | 108 | 88 | 86 | 22 | 22 | 5 mins. |
| I. | 24/5/38 | 160 | 144 | 126 | 110 | 34 | 34 | 5 mins. |
| J. | 9/2/38 | 142 | 132 | 88 | 80 | 54 | 52 | 3 hours |
| | 10/2/38 | 168 | 148 | 110 | 90 | 58 | 58 | 5 mins. |

TABLE 9 (Contd.)

| Name | Date | Systolic Pressure | | Diastolic Pressure | | Pulse Pressure | | Time at which Change Occurred. |
|---|---|---|---|---|---|---|---|---|
| | | Original | After Calcium | Original | After Calcium | Original | After Calcium | |
| K. | 10/3/38 | 120 | 146 | 90 | 115 | 30 | 31 | 5 mins. |
| | 11/3/38 | 118 | 140 | 90 | 100 | 28 | 40 | 5 mins. |
| L. | 10/3/38 | 170 | 182 | 100 | 105 | 70 | 77 | 5 mins. |
| | 11/3/38 | 148 | 148 | 80 | 80 | 68 | 68 | 5 mins. |
| M. | 16/2/38 | 170 | 184 | 100 | 100 | 70 | 84 | 5 mins. |
| N. | 9/2/38 | 140 | 126 | 100 | 90 | 40 | 36 | 5 mins. |
| | 10/2/38 | 154 | 142 | 100 | 95 | 54 | 47 | 5 mins. |
| | 11/2/38 | 146 | 130 | 90 | 82 | 56 | 48 | 5 mins. |
| | 12/2/38 | 134 | 128 | 90 | 86 | 44 | 42 | 5 mins. |
| O. | 4/2/38 | 150 | 126 | 90 | 60 | 60 | 66 | 5 mins. |
| | 5/2/38 | 150 | - | 94 | - | 56 | - | - |
| | 7/2/38 | 160 | 156 | 90 | 80 | 70 | 76 | 5 mins. |
| | 8/2/38 | 150 | 140 | 100 | 80 | 50 | 60 | 5 mins. |
| | 9/2/38 | 124 | 136 | 90 | 76 | 34 | 60 | 5 mins. |
| | 10/2/38 | 156 | - | 100 | - | 56 | - | - |
| | 14/2/38 | 128 | 140 | 90 | 80 | 38 | 60 | 5 mins. |
| P. | 4/2/38 | 152 | 152 | 90 | 90 | 62 | 62 | 1 hour |
| | 5/2/38 | 160 | - | 90 | - | 70 | - | - |
| | 7/2/38 | 184 | 180 | 110 | 90 | 74 | 90 | 5 mins. |
| | 8/2/38 | 154 | - | 78 | - | 76 | - | - |
| | 9/2/38 | 158 | 168 | 100 | 80 | 58 | 88 | 5 mins. |
| Q. | 4/2/38 | 166 | 160 | 100 | 90 | 66 | 70 | 5 mins. |
| | 5/2/38 | 140 | - | 80 | - | 60 | - | - |
| | 7/2/38 | 140 | 150 | 90 | 100 | 50 | 50 | 5 mins. |
| | 8/2/38 | 174 | - | 106 | - | 68 | - | - |
| | 9/2/38 | 154 | 150 | 88 | 80 | 66 | 70 | 5 mins. |
| R. | 8/2/38 | 140 | 128 | 86 | 78 | 54 | 50 | 5 mins. |
| | 9/2/38 | 124 | 136 | 90 | 76 | 34 | 60 | 5 mins. |
| | 10/2/38 | 128 | - | 74 | - | 54 | - | - |
| S. | 6/3/38 | 176 | 178 | 120 | 110 | 56 | 68 | 5 mins. |

TABLE 9 (Contd.)

| Name | Date | Systolic Pressure | | Diastolic Pressure | | Pulse Pressure | | Time at which Change Occurred. |
|---|---|---|---|---|---|---|---|---|
| | | Original | After Calcium | Original | After Calcium | Original | After Calcium | |
| T. | 12/2/38 | 182 | - | 80 | - | 102 | - | - |
| | 13/2/38 | 210 | 220 | 80 | 100 | 130 | 120 | 5 mins. |
| | 14/2/38 | 200 | 176 | 80 | 80 | 120 | 96 | 5 mins. |
| | 16/2/38 | 230 | 214 | 105 | 110 | 125 | 104 | 5 mins. |
| U. | 6/6/38 | 120 | 130 | 80 | 88 | 40 | 42 | 5 mins. |
| | 7/6/38 | 144 | 140 | 90 | 90 | 54 | 50 | 5 mins. |
| | 8/6/38 | 130 | 140 | 84 | 100 | 46 | 40 | 5 mins. |
| | 10/6/38 | 146 | - | 90 | - | 56 | - | - |

These results may be summarised as follows :-

TABLE 10

Changes in Systolic Blood Pressure

| Reduction | | Increase | |
|---|---|---|---|
| Immediate. | Delayed. | Immediate. | Delayed. |
| 17 | 19 | 17 | 19 |

That the blood pressure is equally liable to elevation or lowering after calcium is to be noted from these results. From the table, too, it is obvious that the reaction of the blood pressure to calcium gluconate varies in different patients and in the same patient on different days.

As regards pulse pressure an increase was noted in eighteen cases, a decrease in eleven, and no change greater than 4 millimetres of mercury in the others. Thus, though

there is not the same similarity about the pulse pressures as about the systolic pressures, it is seen that here too the reaction varies in different patients.

Neither the heart rate nor the rhythm were found to have any effect on the direction of either the blood pressure or the pulse pressure.

(g) Effect of Calcium Upon Venous Pressure.

Venous pressure was estimated by the method described by Lewis (30). The vertical distance from an imaginary line drawn outwards from the upper limit of the enlarged and dilated external jugular vein to a parallel imaginary line drawn outwards from near the lower border of the manubrium sterni was taken as a measure of the venous pressure. Measurements were taken five minutes before and at varying intervals after the injection of calcium gluconate. Eighteen investigations of this sort were carried out on eleven patients. The results are shown in the following table, Table 11.

TABLE 11

Showing the Effect of Intravenous Calcium Gluconate on the Venous Pressure.

| Name | Date | Venous Pressure before Calcium in inches | Maximum Fall in inches | Time of Maximum Fall |
|---|---|---|---|---|
| A.1 | 8/11/38 | 2 5/16 | 9/16 | 90 mins. |
| 2 | 9/11/38 | 1 7/8 | 7/16 | 2 mins. |
| 3 | 11/11/38 | 1 1/4 | None | - |
| B.1 | 7/10/38 | 3 1/16 | 9/16 | 4 hours. |
| 2 | 8/10/38 | 2 9/16 | 7/16 | 10 mins. |
| C. | 15/11/38 | 1 7/8 | 5/16 | 5 mins. |
| D. | 18/11/38 | 13/16 | None | - |
| E.1 | 21/11/38 | 2 1/4 | 9/16 | 10 mins. |
| 2 | 22/11/38 | 1 13/16 | 7/16 | 2 hours. |
| 3 | 23/11/38 | 1 7/16 | 1/16 | 2 mins. |
| F. | 16/11/38 | 1 7/8 | None | - |

TABLE 11 (Contd.)

| Name | Date | Venous Pressure before Calcium in inches | Maximum Fall in inches | Time of Maximum Fall |
|---|---|---|---|---|
| G.1 | 4/11/38 | 2 3/16 | 1/8 | 2 mins. |
| 2 | 5/11/38 | 2 3/16 | None | - |
| 3 | 6/11/38 | 2 7/16 | None | - |
| H. | 18/11/38 | 3 3/16 | 1/2 | 2 mins. |
| I. | 19/11/38 | 3 3/16 | 11/16 | 5 mins. |
| J. | 20/11/38 | 2 5/8 | None | - |
| K. | 2/11/38 | 1 1/16 | None | - |

Of the eighteen investigations carried out a fall in venous pressure was noted in eleven. In seven instances there was no change. In no case did the pressure rise. The fall in pressure, when it did occur, was in evidence two minutes after the termination of the injection. The pressure remained lowered for a varying period after the injection, and in some cases on the following day was still below the original level. The time taken for the pressure to reach its lowest level varied between two minutes and four hours in different patients.

It would appear from these results that in the majority of cases a single intravenous injection of calcium gluconate leads to a reduction of venous pressure, an effect which is probably due to an improvement in heart action.

(h) Effect of Calcium on the Respiration.

Hooker (25) noted the effect of the addition of calcium to the perfusing fluid on the frog's brain with special reference to the respiratory centre. He found that when potassium and calcium were both absent the centre was stimulated, whereas in the presence of potassium a decrease of calcium caused depression and an increase caused excitation. Arguing on these lines, and since potassium is present in human serum, one would expect that the administration of calcium would stimulate the centre and lead to an increase in respiration. I was unable to find any reference dealing with the effect of the intravenous injection of a calcium salt on respiration in the human subject. In the present investigation the action of calcium on the respiration was studied in six patients.

The apparatus used was a stethograph consisting of a chest-piece tied round the patient's thorax and communicating by a rubber tube with a small tambour on which was fixed a pointer. The surface of the tambour rose and fell with the respiratory excursion, and these movements were transmitted to the pointer which was arranged to write on a moving drum surface. Unfortunately a time marker was not available but repeated trials showed that the drum which was driven by an electric motor moved

uniformly, and that equal horizontal distances on the surface corresponded to equal intervals of time. In order to make certain that the intravenous injection of 10 c.cs. of fluid apart from calcium had no effect, 10 c.cs. of 0.9% saline was given into the arm vein prior to the administration of the calcium gluconate.

The tracings show the results obtained; these are summarised in Table 12. It is clear that in five out of the six patients the rate was slowed. In the exception, the original rate was the slowest of the group. In three patients the breathing became more regular both as regards time and amplitude. Thus it was noted that both large gasping and small jerky efforts at breathing disappeared. In three patients the amplitude of the respiration was reduced.

Whether the results are due to a direct action of calcium on the respiratory centre or are secondary to improvement in the circulation there is no evidence. The effects, indeed, were not dramatic, and it was not thought worth while to pursue this line of investigation. It was obvious that in order to produce more marked changes in the respiration larger amounts of calcium would be required, a procedure fraught with some risk to the patient.

In the following table the number of respirations per minute are shown. Actually the number of respirations in eight centimetres of the tracings both before and after the

calcium injection was counted. This length gave a sufficiency of respirations (the number in 2 2/3 minutes) to allow any differences in rate to be appreciated.

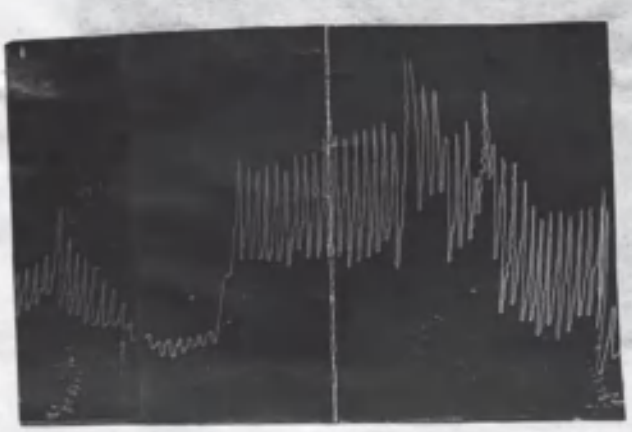
TABLE 12

Showing the Effect of Intravenous Calcium Gluconate on the Respiration.

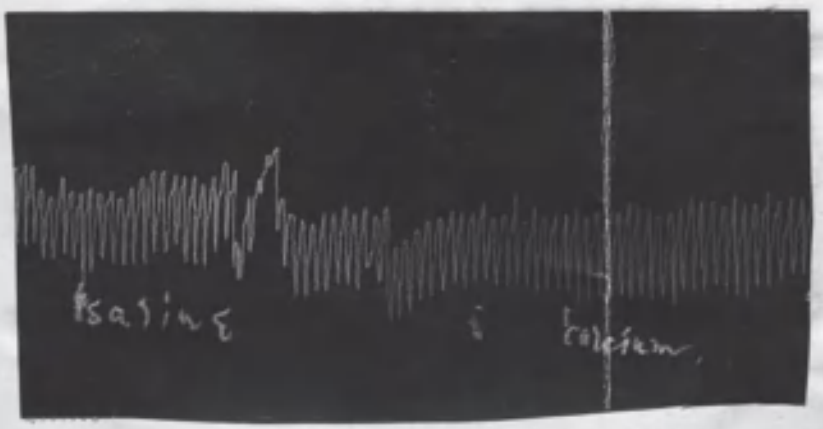
| Name | Rate per Minute before Calcium | Rate per Minute after Calcium | Regularity | Amplitude |
|---|---|---|---|---|
| A. | 22 | 20 | Increased | No Change |
| B. | 19 | 17 | No Change | Diminished |
| C. | 20 | 19 | Increased | Diminished |
| D. | 31 | 29 | Increased | No Change |
| E. | 12 | 12 | No Change | No Change |
| F. | 24 | 21 | No Change | Diminished |

The tracings are shown in the following pages.

A. 3/10/38.



Before Calcium.



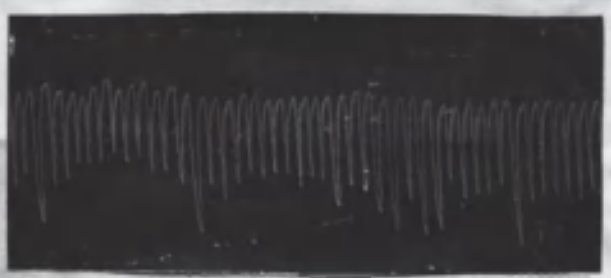

During Calcium.

After Calcium.

B. 6/10/38.

Before Calcium.

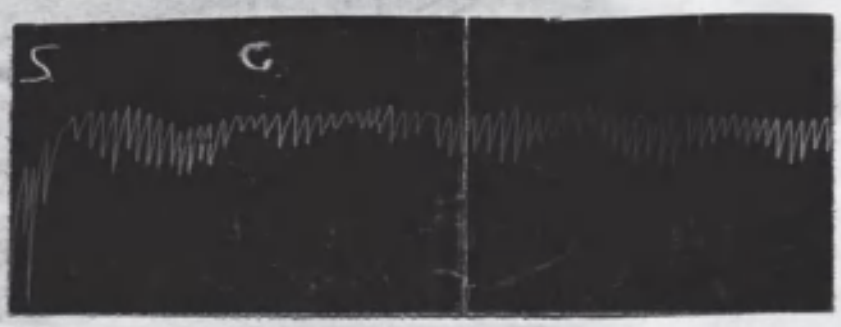
During Calcium.



After Calcium.

C. 25/9/38.

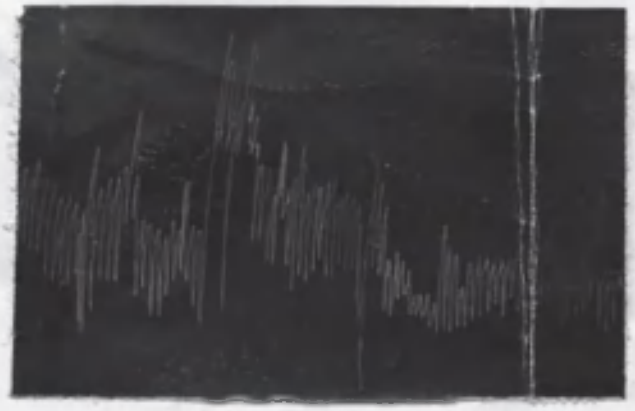
Before Calcium.



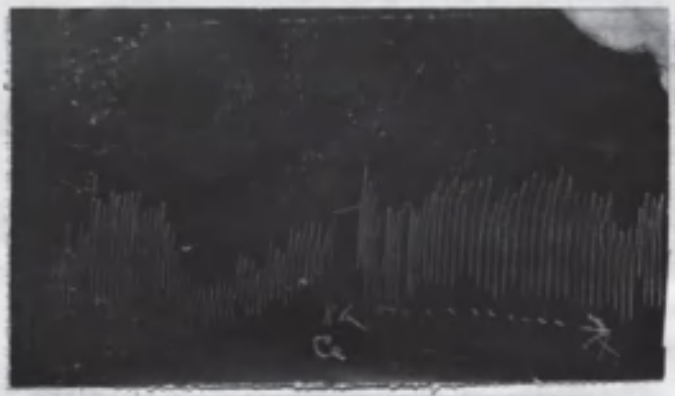

During Calcium.

After Calcium.

D. 22/11/38.



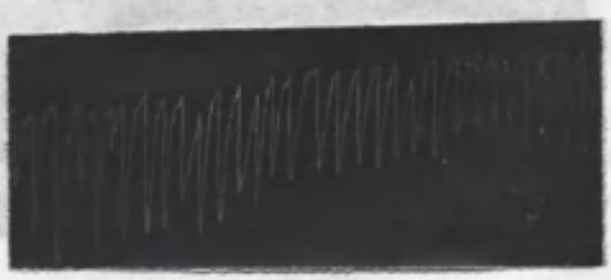
Before Calcium.




During Calcium.

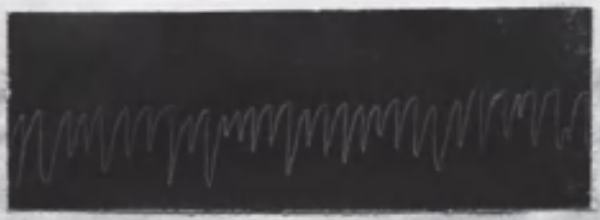
After Calcium.

E. 7/11/38.



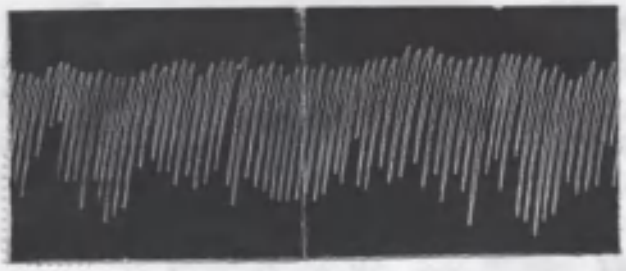
Before Calcium.


During Calcium.



After Calcium.

F. 5/10/38.



Before Calcium.


During Calcium.

After Calcium.

(i) Effect of Calcium on the Viscosity of the Blood.

There is no doubt that the viscosity of the blood is a factor in the amount of work requiring to be done by the heart in the propulsion of blood through the peripheral vessels. Any decrease in the viscosity of the blood would naturally lighten the work of the heart and to that extent would be advantageous when there was cardiac fatigue or debility.

A. Viscosity of the Blood in Cardiac Failure.

Markson (37) found that in twenty out of twenty-six patients with cardiac failure the blood viscosity was increased. Oedematous patients tended to have a low blood viscosity. Recovery from congestive heart failure, he stated, is associated with a reduction in the viscosity of the blood, but, when there was marked oedema, the subsidence of the oedema was accompanied by an increase in viscosity.

In the present work the blood viscosity was determined in thirty-five patients with cardiac failure and in fifty patients in whom no evidence, subjective or objective, of heart disease could be detected. The instrument used was the viscosimeter of Hess and all necessary precautions as regards temperature etc. were taken. In the group without cardiac disease the average blood viscosity was 4.7. The results are summarised in Table 13.

TABLE 13

The Blood Viscosity (Maximum, Minimum and Average) in Fifty Patients Suffering from some Disease other than Cardiac Failure.

| Disease | Number of Cases | Blood Viscosity | | |
|---|---|---|---|---|
| | | Maximum | Minimum | Average |
| 1. Hypochromic microcytic anaemia. | 12 | 4.9 | 3.8 | 4.3 |
| 2. Lesions of the nervous system. | 5 | 5.4 | 3.9 | 4.5 |
| 3. In association with pyrexia (erysipelas, pleurisy, rheumatism etc.). | 8 | 6.5 | 4.9 | 5.5 |
| 4. Hyperpiesis. | 9 | 6.1 | 4.1 | 4.5 |
| 5. Miscellaneous. (Sciatica, myxoedema, bronchitis, jaundice, diabetes, mellitus etc.) | 16 | 6.4 | 4.3 | 5.0 |

The patients with heart failure are divided into four groups :-

(a) peripheral congestion but no oedema,

(b) oedema but no peripheral congestion,

(c) oedema and peripheral congestion,

(d) neither oedema nor peripheral congestion; dyspnoea and pallor the main features.

In all, thirty-five patients had the blood viscosity

determined on admission; serial determinations were also carried out on these patients throughout their course of treatment. In the following table the viscosities on admission are summarised. The actual figures and the serial figures obtained during treatment as the objective signs changed are shown in the appendix.

TABLE 14

| Type | Number of Cases | Blood Viscosity | | |
|---|---|---|---|---|
| | | Maximum | Minimum | Average |
| Peripheral congestion : no oedema. | 13 | 9.1 | 4.2 | 6.3 |
| Oedema : no peripheral congestion. | 2 | 3.9 | 3.7 | 3.8 |
| Oedema and peripheral congestion. | 18 | 7.3 | 3.3 | 5.1 |
| Neither oedema nor peripheral congestion. Dyspnoea and pallor the main features. | 2 | 5.2 | 4.5 | 4.8 |

There is no doubt from these figures that in patients with heart failure and no oedema the blood viscosity is raised. Furthermore, serial estimations indicate that in this group clinical improvement is associated with a fall in viscosity, clinical deterioration with a rise.

This may be best shown by the following examples of two patients on routine treatment for cardiac failure.

TABLE 15

Showing Relation of Blood Viscosity to Degree of Venous Congestion as Indicated by Cyanosis in Patients under Routine Treatment for Cardiac Failure.

| Name | Date | Cyanosis | Blood Viscosity | Remarks |
|---|---|---|---|---|
| G.H. | 21/12/37 | +++ | 6.5 | General symptomatic and clinical improvement was associated with the fall in viscosity. |
| | 22/12/37 | ++ | 5.3 | |
| | 4/1/38 | ++ | 4.7 | |
| | 15/1/38 | ++ | 5.2 | |
| | 24/1/38 | + | 4.6 | |
| | 9/3/38 | - | 4.2 | |
| Q. | 25/5/38 | + | 4.9 | Worsening of clinical condition and increase of cyanosis associated with an increase of viscosity. |
| | 27/5/38 | + | 4.8 | |
| | 28/5/38 | ++ | 5.4 | |

When there was oedema but little evidence of venous congestion or stasis the viscosity was low. It would appear therefore that in cardiac failure the viscosity of the blood is influenced in opposed directions by venous congestion and oedema. Accordingly it would be expected that in patients with marked oedema but little or no peripheral stasis the viscosity would rise during the course of successful treatment. This, indeed, is what actually takes place as can be seen from the following examples.

TABLE 16

Showing Relation of Blood Viscosity to Degree of Oedema in Patients under Routine Treatment for Cardiac Failure.

| Name | Date | Oedema | Blood Viscosity | Remarks |
|---|---|---|---|---|
| S. | 12/2/38 | ++ | 3.3 | Rise of blood viscosity associated with clearing of oedema. |
| | 16/2/38 | + | 3.4 | |
| | 10/3/38 | - | 3.9 | |
| Z. | 17/12/37 | ++++ | 4.3 | Gradual rise of viscosity with subsidence of oedema till a high reading was reached: this was associated with a marked degree of congestion as indicated by cyanosis. The viscosity fell rapidly when the congestion was relieved. |
| | 6/1/38 | +++ | 4.4 | |
| | 25/1/38 | ++ | 4.9 | |
| | 3/2/38 | - | 7.2 | |
| | 11/2/38 | - | 4.9 | |

Where both peripheral congestion and oedema are present, the change in blood viscosity is naturally dependent on the relative importance of these two factors in the individual patient.

B. Effect of Intravenous Administration of Calcium Gluconate on the Viscosity of the Blood.

The viscosity of the blood was determined in six healthy subjects before and on several occasions after the intravenous administration of calcium gluconate. In none was there a difference in value greater than 0.2. These results are shown in Table 17.

TABLE 17

Effect of Intravenous Calcium Gluconate on the Blood Viscosity in Six Healthy Subjects

| Name | Date | Blood Viscosity | | Time after Calcium. | Difference in Viscosity. |
|---|---|---|---|---|---|
| | | Before Calcium | After Calcium | | |
| A. | 5/5/38 | 5.0 | 5.0 | 5 mins. | - |
| | | | 5.0 | 15 mins. | - |
| | | | 5.1 | 1 hour | .1 |
| B. | 5/5/38 | 4.8 | 4.8 | 5 mins. | - |
| | | | 4.8 | 15 mins. | - |
| | | | 4.6 | 1 hour | .2 |
| | | | 4.8 | 4 hours | - |
| C. | 5/5/38 | 4.4 | 4.4 | 5 mins. | - |
| | | | 4.4 | 15 mins. | - |
| | | | 4.3 | 1 hour | .1 |
| D. | 6/5/38 | 4.3 | 4.3 | 15 mins. | - |
| | | | 4.4 | 50 mins. | .1 |
| E. | 6/5/38 | 4.5 | 4.3 | 15 mins. | .2 |
| | | | 4.3 | 50 mins. | .2 |
| | | | 4.5 | 24 hours | - |
| F. | 6/5/38 | 3.8 | 3.6 | 15 mins. | .2 |
| | | | 3.8 | 50 mins. | - |

The effect of calcium on the blood viscosity was also determined in twenty patients with cardiac failure. These results are shown in Table 18.

TABLE 18

Effect of Intravenous Calcium Gluconate on the Blood Viscosity in Twenty Patients with Cardiac Failure

| Name | Date | Oed. | Cyan. | Blood Viscosity | | Time after Calcium | Difference in Viscosity |
|---|---|---|---|---|---|---|---|
| | | | | before Calcium | after Calcium | | |
| A. | 4/4/38 | ++++ | + | 4.7 | 4.7 | 15 mins. | - |
| | 5/4/38 | | | 5.3 | 4.8 | 20 mins. | -.5 |
| | 6/4/38 | | | 4.9 | 4.5 | 15 mins. | -.4 |
| | 7/4/38 | | | 4.3 | 4.4 | 15 mins. | +.1 |
| B. | 24/3/38 | ++ | + | 4.5 | 4.1 | 5 mins. | -.4 |
| | | | | | 4.1 | 4 hours | -.4 |
| | 5/4/38 | | | 5.3 | 4.8 | 15 mins. | -.5 |
| C. | 28/3/38 | - | ++ | 6.8 | 6.4 | 5 mins. | -.4 |
| | 30/3/38 | | | 5.4 | 5.2 | 5 mins. | -.2 |
| | 31/3/38 | | | 5.7 | 5.6 | 5 mins. | -.1 |
| D. | 25/3/38 | - | ++ | 6.8 | 6.1 | 5 mins. | -.7 |
| | | | | | 6.1 | 1 hour | -.7 |
| E. | 18/3/38 | - | ++ | 5.4 | 5.1 | 5 mins. | -.3 |
| F. | 9/5/38 | +++ | + | 3.6 | 3.6 | 18 mins. | - |
| | | | | | 3.6 | 2 hours | - |
| | 11/5/38 | | | 3.5 | 3.1 | 5 mins. | -.4 |
| | 12/5/38 | | | 3.7 | 3.6 | 4 hours | -.1 |
| | 13/5/38 | | | 3.6 | 3.6 | 5 mins. | - |
| | 16/5/38 | | | 3.6 | 3.4 | 3 hours | -.2 |
| G. | 27/5/38 | +++ | + | 5.4 | 5.3 | 5 mins. | -.1 |
| | | | | | 4.8 | 4 hours | -.6 |
| | 28/5/38 | | | 5.5 | 4.2 | 1 hour | -1.3 |
| H. | 24/3/38 | +++ | - | 5.9 | 6.1 | 5 mins. | +.2 |
| I. | 21/4/38 | - | +++ | 6.2 | 5.8 | 5 mins. | -.4 |
| | | | | | 5.8 | 1 hour | -.4 |

TABLE 18 (Contd.)

| Name | Date | Oed. | Cyan. | Blood Viscosity before Calcium | Blood Viscosity after Calcium | Time after Calcium | Difference in Viscosity |
|---|---|---|---|---|---|---|---|
| J. | 18/2/38 | + | + | 5.3 | 5.1 | 1 hour | -.2 |
| | 19/2/38 | | | 5.1 | 5.0 | 5 mins. | -.1 |
| K. | 17/3/38 | - | +++ | 7.1 | 6.0 | 5 mins. | -1.1 |
| | | | | | 6.2 | 10 mins. | -.9 |
| | | | | | 6.2 | 1 hour | -.9 |
| | 18/3/38 | | | 6.3 | 6.2 | 1 hour | -.1 |
| | 10/4/38 | | | 5.9 | 5.9 | 1 hour | - |
| L. | 3/6/38 | + | + | 4.3 | 4.3 | 5 mins. | - |
| | | | | | 4.3 | 1 hour | - |
| M. | 7/5/38 | +++ | - | 3.9 | 3.6 | 5 mins. | -.3 |
| | | | | 3.6 | 3.4 | 5 mins. | -.2 |
| | | | | | 3.4 | 5 mins. | -.2 |
| N. | 10/6/38 | ++ | - | 3.5 | 3.8 | 5 mins. | +.3 |
| | | | | | 3.6 | 1 hour | +.1 |
| | | | | 3.6 | 3.8 | 1 hour | +.2 |
| O. | 6/4/38 | - | ++ | 8.2 | 6.9 | 5 mins. | -1.3 |
| | | | | | 7.0 | 1 hour | -1.2 |
| | | | | | 6.9 | 2 hours | -1.3 |
| | 7/4/38 | | | 7.4 | 6.9 | 5 mins. | -.5 |
| | | | | | 6.9 | 1 hour | -.5 |
| | 10/4/38 | | | 6.3 | 6.2 | 1 hour | -.1 |
| | 16/5/38 | | | 5.8 | 5.8 | 5 mins. | - |
| | | | | | 5.8 | 1 hour | - |
| P. | 7/3/38 | - | ++ | 6.1 | 5.3 | 1 hour | -.8 |
| Q. | 4/2/38 | +++ | - | 4.0 | 4.4 | 5 mins. | +.4 |
| | | | | | 4.3 | 1 hour | +.3 |
| R. | 17/4/38 | + | + | 4.8 | 4.8 | 5 mins. | - |
| | | | | | 4.8 | 1 hour | - |
| S. | 8/7/38 | ++ | + | 4.1 | 4.3 | 1 hour | +.2 |
| | | | | | 4.3 | 2 hours | +.2 |
| | 9/7/38 | | | 4.4 | 4.1 | 1 hour | -.3 |
| | | | | | 4.1 | 2 hours | -.3 |
| | 17/7/38 | | | 4.0 | 4.2 | 1 hour | +.2 |
| T. | 23/3/38 | - | ++ | 6.8 | 6.2 | 5 mins. | -.6 |
| | | | | | 5.9 | 1 hour | -.9 |
| | | | | | 6.0 | 2 hours | -.8 |
| | 30/3/38 | | | 5.4 | 5.4 | 1 hour | - |

A change of the viscosity value below 0.3 was neglected as being due to a normal variation. When the patients are grouped according to the presence of oedema and peripheral congestion, it is seen that in all those with stasis but no evidence of oedema the viscosity was reduced after the injection of calcium. In the other two groups, comprising those showing oedema with and without signs of peripheral congestion, the results varied, some indicating a fall, some a rise, and some no change of viscosity. The two patients in whom a rise occurred had signs of gross oedema.

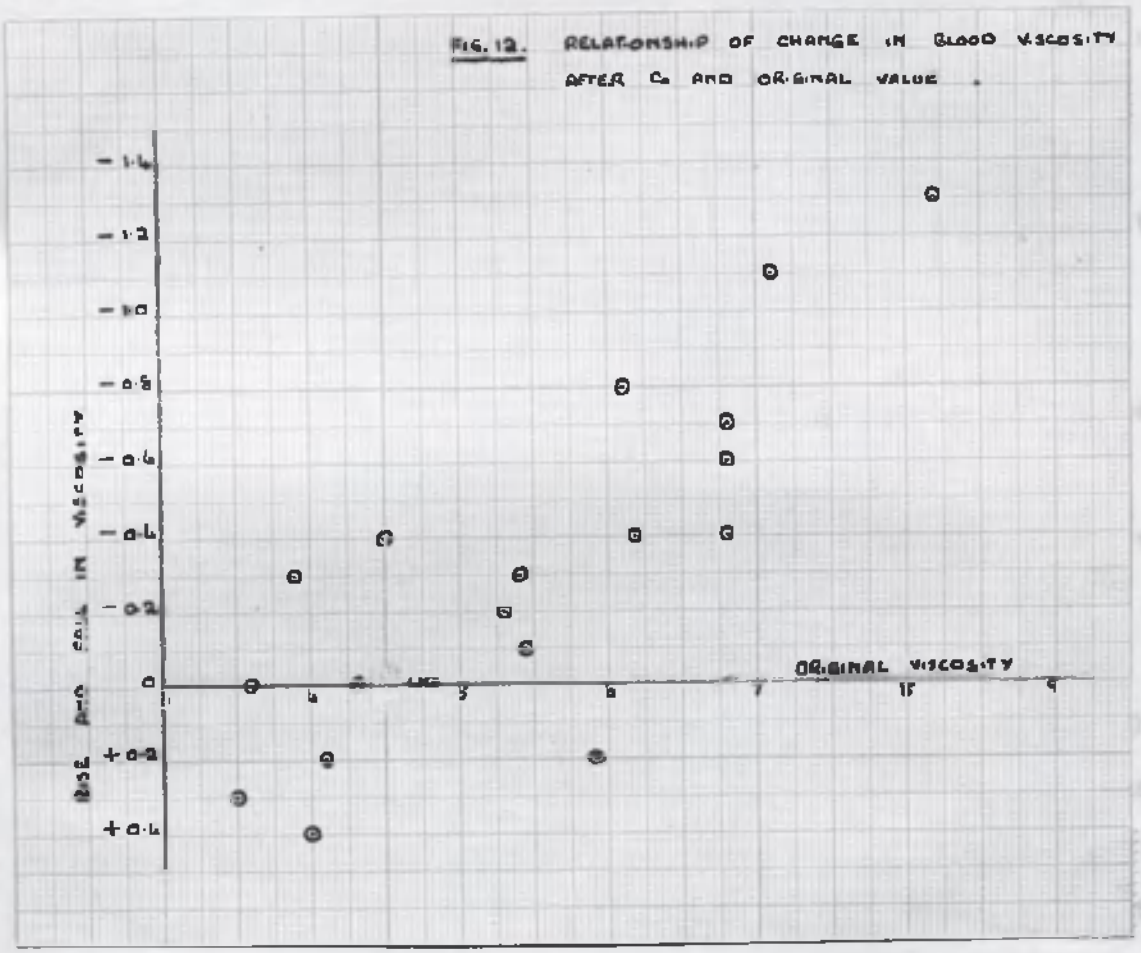
It will be seen from Table 18 that in all thirty-nine estimations of blood viscosity were done on the twenty patients before the various calcium injections and sixty-two after the injections. The results are summarised in the following table, Table 19.

TABLE 19

Change of Blood Viscosity in Patients with Cardiac Failure after Administration of Calcium Gluconate

| Blood Viscosity | Stasis Alone | Oedema Alone | Stasis with Oedema |
|---|---|---|---|
| Fall | 8 | 1 | 5 |
| No Change | - | 1 | 3 |
| Rise | - | 2 | - |

It is obvious from the following figure, Fig. 12, that there is a slight degree of correlation between the original height of the viscosity and the reduction after the intravenous injection of calcium.




There appears to be little doubt that in patients with marked peripheral stasis there is a fall in blood viscosity after the injection of calcium. The high

viscosity found in this type of patient is almost certainly due to the increase in the number of red cells in the peripheral circulation. The reduction in the viscosity can reasonably be attributed to a fall of red cell volume in the capillaries due to the increasing efficiency of the heart as a force pump.

Where oedema is the marked feature, a greater cardiac efficiency would again tend to produce a more rapid movement of the cells through the peripheral circulation. In this type of case, however, another factor has to be considered, namely, the presence of an abnormal amount of fluid. There is some evidence that in the presence of oedema of cardiac origin the blood is more hydraemic than usual. Furthermore, it has been suggested that, as a result of peripheral anoxaemia, the walls of the capillaries are rendered more permeable, allowing protein-containing fluid to pass through the vascular endothelium. The passage of fluid through the capillary wall is regulated by such factors as osmotic pressure, colloid and crystalloid, and tissue elasticity, but there is no doubt that among these must be considered the force exerted by the blood pressure. An increase in the efficiency of the heart will lead to a rise in peripheral blood pressure and may be sufficient to force through the capillary walls a certain amount of plasma, especially since the endothelial permeability is increased. With increased circulatory efficiency, too, urinary output is increased. By one or both methods fluid tends to pass

from the blood stream, so that the percentage red cell volume tends to rise with resultant increase in blood viscosity.

In cardiac failure with or without oedema the changes in blood viscosity after calcium administration may reasonably be attributed to the cardiotonic action of this element. It would appear, however, that the beneficial effect is more marked in patients in whom peripheral congestion is a marked feature. In these subjects the fall in blood viscosity lightens the work of the heart and thus promotes its further recovery.

(j) Effect of Calcium on Diuresis.

One of the main objects of therapeutics in many patients with cardiac failure is to get rid of large collections of oedema fluid. Calcium chloride has, for some time now, been used as a diuretic, but the view generally held is that it owes its efficiency in this respect to the fact that it is an acid-producing salt, and that the diuresis is to be attributed to a shift in acid-base equilibrium to the acidotic side. Much of the previous investigation on the diuretic action of calcium in cardiac oedema was carried out with calcium chloride. In the present work, however, it was desired to investigate the possible effect of calcium itself unassociated with any tendency to produce acidosis. Accordingly calcium gluconate was used at first; later on in the investigation, parathyroid extract was employed to raise the concentration of calcium in the blood.

A. Diuretic Action of Calcium Gluconate.

This was investigated in ten patients with cardiac oedema. The calcium gluconate was administered intravenously in doses of 10 c.cs. of a 10% solution once daily for several days. Prior to the calcium therapy the daily urinary output was measured, and this procedure was continued during the period of digitalis medication following calcium. The fluid intake of each patient was kept constant.

The results are given in Table 20.

TABLE 20

Effect of Various Forms of Therapy on Urinary Output.

| Name | Number of Days | Treatment | Urinary Output in c.cs. (Daily Average) |
|---|---|---|---|
| A. | 7 | Calcium | 1910 |
| | 30 | Digitalis | 2200 |
| B. | 50 | Digitalis Salyrgan | 790 |
| | 21 | Calcium | 640 |
| | 42 | Nil | 640 |
| | 6 | Calcium | 700 |
| | 22 | Digitalis | 700 |
| C. | 42 | Digitalis Salyrgan | 1420 |
| | 3 | Calcium | 1280 |
| | 35 | Digitalis | 1480 (average for first eight days) |
| | | | 2380 (thereafter) |
| D. | 52 | Digitalis Salyrgan | 1600 |
| | 4 | Calcium | 1480 |
| | 29 | Digitalis | 1860 (average for first seven days) |
| | | | 2260 (thereafter) |

TABLE 20 (Contd.)

| Name | Number of Days | Treatment | Urinary Output in c.cs. (Daily Average) |
|---|---|---|---|
| E. | 21 | Digitalis Diuretin | 580 |
| | 3 | Intra-venous Glucose | 700 |
| | 15 | Calcium | 670 |
| | 30 | Digitalis | 750 |
| F. | 26 | Digitalis | 1250 |
| | 6 | Calcium | 1570 |
| | 8 | Digitalis | 1830 |
| G. | 154 | Digitalis | 1300 |
| | 6 | Digitalis Calcium | 1770 |
| H. | 12 | Digitalis | 1450 |
| | 3 | Calcium | 1510 |
| | 10 | Digitalis | 1860 |
| I. | 5 | Rest in Bed | 1390 |
| | 10 | Calcium | 1600 |
| J. | 24 | Digitalis Salyrgan | 490 |
| | 3 | Digitalis Calcium | 610 |
| | 18 | Digitalis Salyrgan | 870 |
| | 3 | Calcium | 750 |

It is obvious that calcium administration has little direct effect on the urinary output, at any rate when compared to the diuresis produced by digitalis. Of the ten patients investigated conclusions as to the diuretic action alone as compared with other forms of therapy (omitting the effect of adding calcium to digitalis) can be drawn from seven. Two, C. & D., showed a slightly decreased excretion of urine and the remaining five, B., E., F., H., and I., an increase. In case A. the output from calcium is less than that from digitalis, but, as is to be described, the digitalis output may have been influenced by the previous course of calcium. In case G. the addition of calcium to simultaneous digitalis therapy (in a very ill patient where such a procedure was considered justifiable) led to an increase in urine passed, but this cannot definitely be ascribed solely to the action of the calcium. No conclusions as to the diuretic action of calcium can be drawn from case J.

In only one of the five cases in which the output was increased did the increase exceed 250 c.cs. Taken as a percentage of the original urinary output, or of the output when no treatment was being given as in case B., the figures for the increased diuresis are :-

-10 : -7 : +9 : +15 : +25 : +4 : +15.

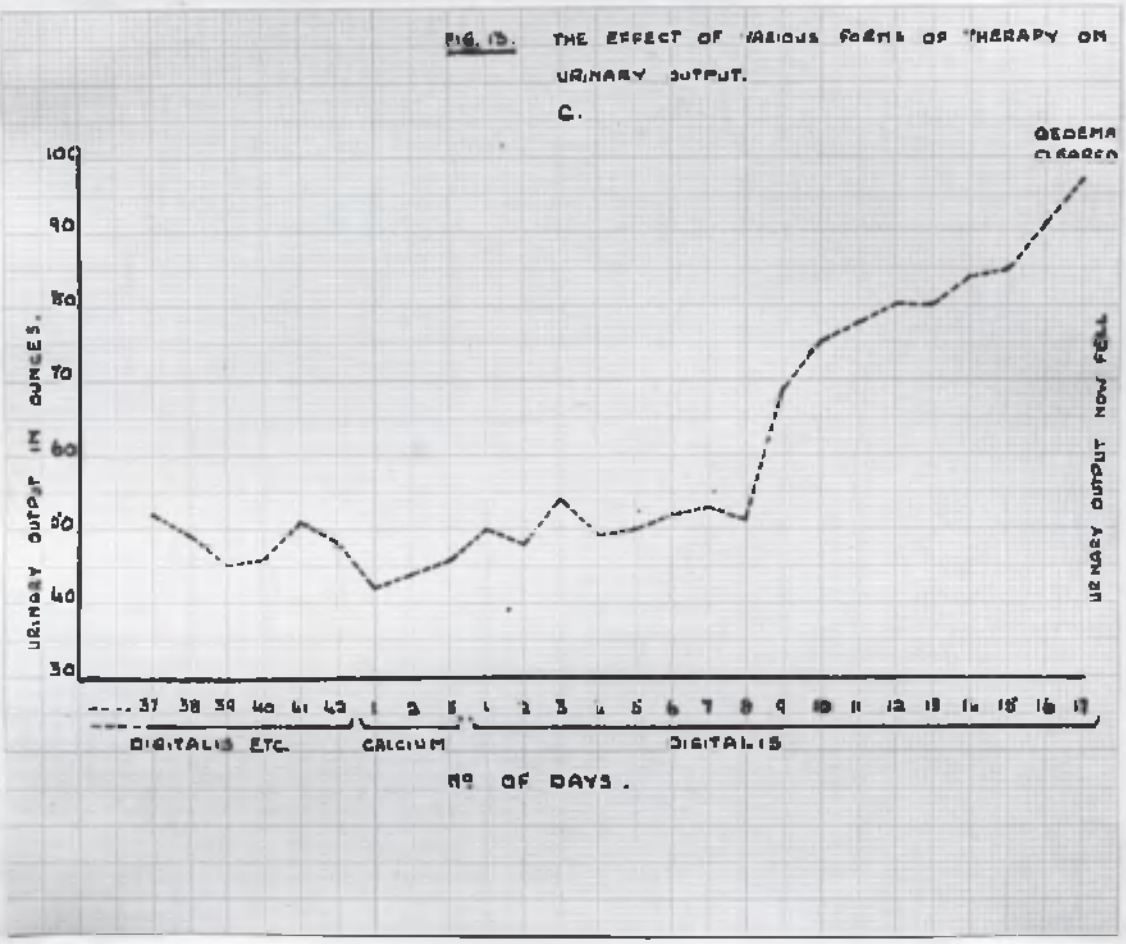
These may be considered as evidence of some diuretic action of calcium, but in view of the large amounts of oedematous fluid present in these patients, one must admit that the direct

diuretic action of calcium, if present at all, is only of academic importance and of little practical value in the treatment of cardiac failure.

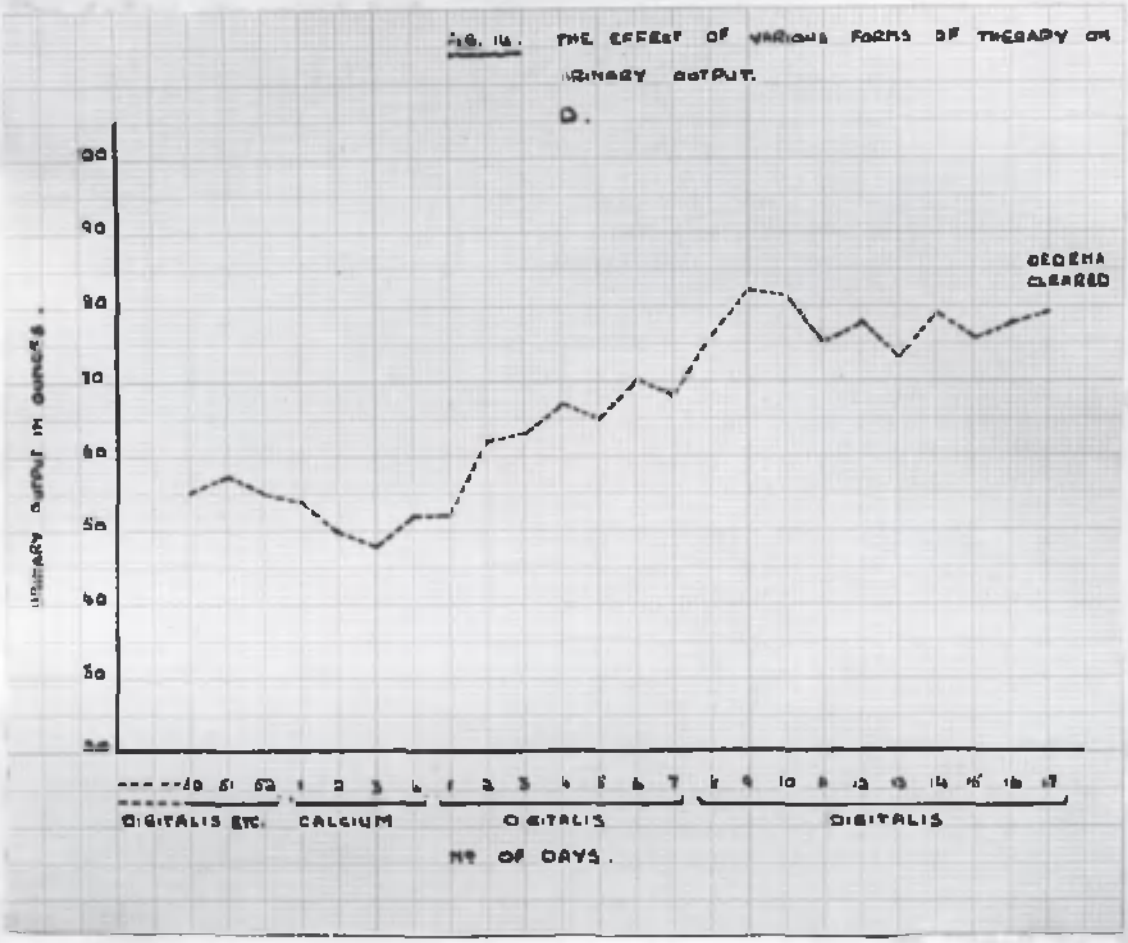
A point of considerable interest, however, is the strengthening of the diuretic effect of digitalis when that drug is given after a course of injections of calcium gluconate. This was done in seven cases and in six of them there was an increased output of urine. In five the increase exceeded 250 c.cs. In these six instances the daily output of urine during the course of digitalis after calcium therapy greatly exceeded the output during the first period of digitalis medication. When the increase is taken as a percentage of the urinary volume during calcium therapy the figures obtained are: C. + (16:85) : D. + (25:52) : E. + 12 : F. + 17 : H. + 23 : J. + 43.

In two patients, C. and D., a peculiar delayed effect was evident.

Case C : During the three days of calcium therapy there was a decrease in the daily output of urine as compared with the figures obtained during a period of forty-two days on digitalis and salyrgan. Immediately after digitalis was recommenced, this time without salyrgan, the urinary output increased and eight days later increased still further. This is shown in the following figure, Fig. 13.




Case D : This patient presents almost exactly the same findings, showing an immediate increase in urinary output on commencing the second course of digitalis and a still further increase seven days later.




The results obtained following injection of calcium gluconate are unlikely to be due to any direct action of the calcium on the renal mechanism or on the tissue exchanges of fluid. If such had been the case one would have expected a more pronounced effect during the period of calcium medication rather than during the subsequent course of digitalis. It would appear, therefore, that calcium sensitises the heart to the therapeutic action of digitalis. Some support is lent to this view by the findings obtained in cases C. and D.

The delay observed before the maximum diuresis occurred during the second course of digitalis suggests that the full cardiotonic effect of this drug was the real cause of the marked rise in urinary volume. The fact that previous administration of digitalis for periods of forty-two and fifty-two days respectively had been unable to achieve this suggests that the ultimate success was due to sensitisation of the myocardium by calcium to the action of digitalis.

B. The Action of Parathyroid Extract on Urinary Output in Cardiac Failure.

Although the results recorded in the previous section appeared to indicate that calcium had little effect on urinary output apart from that produced by strengthening the force of the heart beat, either directly or by potentiating the action of digitalis, it would be unfair to assume on the basis of these findings that calcium had no direct action on renal function. There is, indeed, some evidence that calcium plays a part in the regulation of water metabolism. When, during the perfusion of frogs there is a deficiency of calcium in the fluid, oedema is rapidly produced - H.J. Hamburger, quoted Sollman (49). Luff (35) attributed the anti-oedema effect of calcium to the production of increased coagulability, but Chiari and Januschke (13) found evidence of it even when the blood was rendered incoagulable by hirudin.

Clinicians have remarked on the association of hypocalcaemic tetany of the early years of life and oedema. Thus Bratusch-Marrain ( 7 ) observed the appearance of

spasmophilia while water was being retained and its disappearance during diuresis. Ulmer (51) noted a parallelism between increase of weight and galvanic hyperexcitability whereas recovery from the spasmophilic state was accompanied by an increase in the output of urine. Freudenberg (20) specifically mentions that the oedema associated with tetany is not confined to the hands and feet, but is found elsewhere in the body and is certainly not due to local pressure exerted by the spasm of muscles on the blood vessels. The work of Salvesen (45), and Graham and Oakley (23), and unpublished results of Hutchison and Morris (26) indicate that calcium may exert a beneficial influence on renal function especially when it is impaired.

These considerations seemed to make it worth while investigating the effect of a prolonged rise of serum calcium on the oedema of cardiac failure. In order to achieve hypercalcaemia, injections of parathyroid extract were employed. The preparation actually used was parathormone (Lilly) which was given intramuscularly or intravenously in doses of 20 units daily. The effect of daily parathormone injections on the urinary output was investigated in six patients. The results in each case are discussed separately.

In the first patient (K) the output under various forms of therapy is shown in the following table, Table 21.

TABLE 21

Showing the Effect of Various Forms of Therapy on the Urinary Output.

| Name | Date | Therapy | Output of Urine in c.cs. (Daily Average) |
|---|---|---|---|
| K. | 23/5/38-30/5/38 | Digitalis & Salyrgan | 1480 |
| | 3/6/38-9/6/38 | Calcium Gluconate | 1190 |
| | 9/6/38-17/6/38 | Nil | 1040 |
| | 17/6/38-25/6/38 | Parathormone & Salyrgan | 1940 |
| | 25/6/38-6/7/38 | Salyrgan | 930 |

The output between 17/6/38 and 25/6/38 when parathormone and salyrgan were being given is shown in detail as under :-

| Date | Therapy | Output in c.cs. |
|---|---|---|
| 17/6/38 | P. | 640 |
| 18/6/38 | - | 870 |
| 19/6/38 | P. & S. | 5070 |
| 20/6/38 | - | 320 |
| 21/6/38 | P. & S. | 3710 |
| 22/6/38 | P. | 1540 |
| 23/6/38 | P. | 210 |
| 24/6/38 | P. & S. | 4440 |
| 25/6/38 | P. | 810 |

P..... Parathormone : S..... Salyrgan

When the results are collated for the various types of therapy it is seen that the output was much the greatest during parathormone administration. During the digitalis period, when salyrgan was given in doses of 1 c.c. every second day,

the maximum daily output of urine was 1840 c.cs. with an average of 1480 c.cs., whereas in the parathormone period when salyrgan was given in the same dosage as in the first period, the average daily excretion of urine was 1940 c.cs. with a maximum of 5070 c.cs. Prior to the commencement of parathyroid therapy the serum calcium was 9.1 mgrms.%, during the parathormone period 12.2 mgrms.%. After the cessation of parathormone administration the serum calcium fell to reach the level of 10.4 mgrms.% in eleven days. Coincident with this there was noted a reduction in the daily output of urine although the injections of salyrgan were continued every second day.

In the next case the daily output of urine is shown throughout the period of investigation.

TABLE 22

| Name | Period | Date | Therapy | Output of Urine in c.cs. (Daily Average) | Serum Calcium mgrms. % |
|---|---|---|---|---|---|
| L. | 1. | 24/9/38 | S. | 2780 | |
| | | 25/9/38 | S. | 2440 | |
| | | 26/9/38 | S. | 2200 | |
| | | 27/9/38 | S. | 1160 | 10.6 |
| | 11. | 28/9/38 | S. & P. | 1450 | |
| | | 29/9/38 | S. & P. | 1970 | |
| | | 30/9/38 | S. & P. | 2090 | |
| | | 1/10/38 | S. & P. | 2030 | |
| | | 2/10/38 | S. & P. | 2320 | |
| | | 3/10/38 | S. & P. | 2090 | 12.6 |

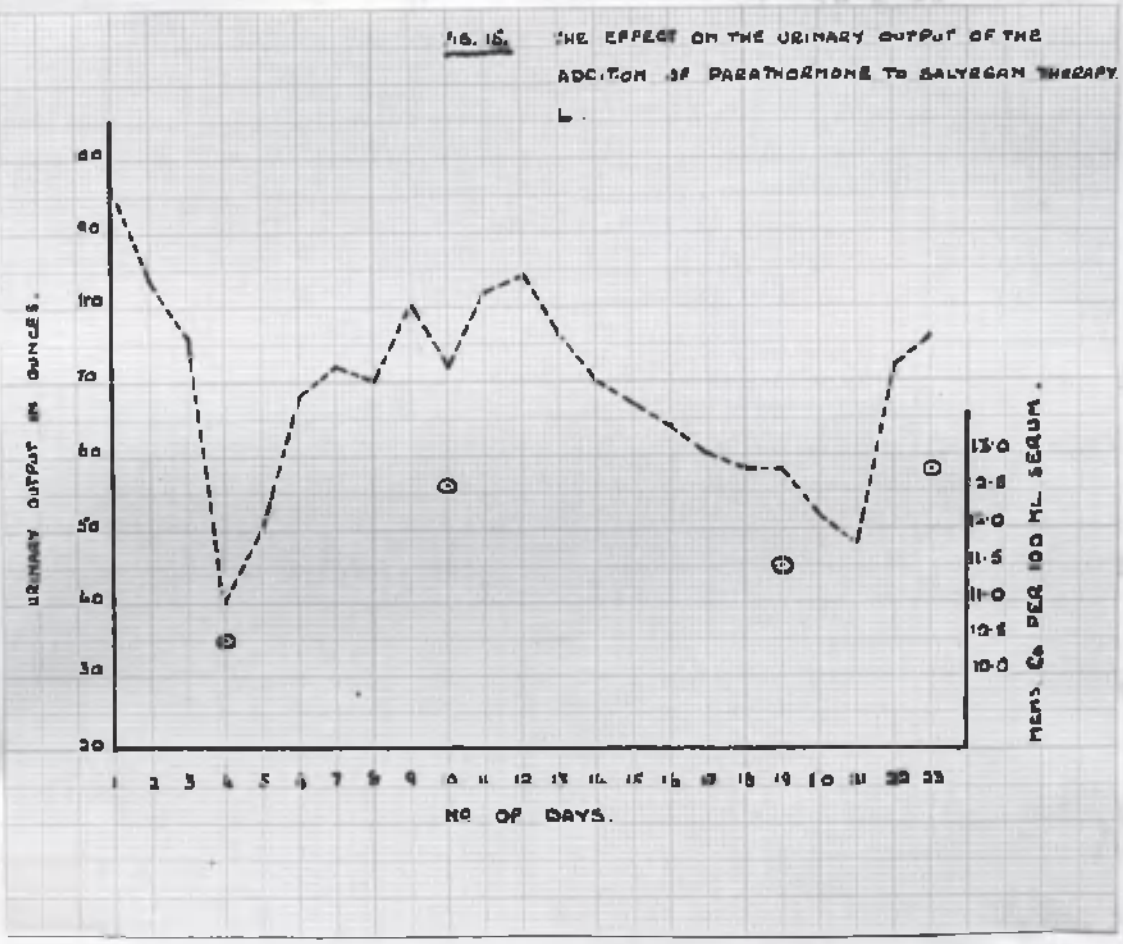
TABLE 22 (Contd.)

| Name | Period | Date | Therapy | Output of Urine in c.cs. (Daily Average) | Serum Calcium mgrms.% |
|---|---|---|---|---|---|
| | 111. | 4/10/38 | S. | 2380 | |
| | | 5/10/38 | S. | 2440 | |
| | | 6/10/38 | S. | 2200 | |
| | | 7/10/38 | S. | 2030 | |
| | | 8/10/38 | S. | 1940 | |
| | | 9/10/38 | S. | 1860 | |
| | | 10/10/38 | S. | 1740 | |
| | | 11/10/38 | S. | 1680 | |
| | | 12/10/38 | S. | 1680 | 11.5 |
| | 1V. | 13/10/38 | S. & P. | 1510 | |
| | | 14/10/38 | S. & P. | 1390 | |
| | | 15/10/38 | S. & P. | 2090 | |
| | | 16/10/38 | S. & P. | 2200 | 12.8 |

S..... Salyrgan : P..... Parathormone

It is well known that with continued administration of salyrgan less and less diuretic effect tends to be produced. With this patient the aim of the investigation was to determine whether parathormone injections could increase the diuretic effect of salyrgan when on the wane. The investigation may conveniently be divided into four periods. The first shows the usual diuretic action of salyrgan. In the second, parathormone was given with salyrgan, and it is evident that the urinary output was increased to reach a level approaching that obtained with salyrgan at the peak of its diuretic effect. In the third period salyrgan was again given alone, and it will be noted that a very good diuretic action persisted for the first few days, but that this steadily diminished as time went on. After nine days parathormone therapy was again

commenced and during this, the fourth period, the urinary output again increased. These findings are presented in Fig. 15 which shows a definite degree of parallelism between the urinary volume and the level of serum calcium.



The average daily output of urine in the next case is shown in the following table.

TABLE 23

| Name | Date | Therapy | Urinary Output in c.cs. (Daily Average) |
|---|---|---|---|
| M. | 21/9/38-24/9/38 | Nil | 1070 |
| | 25/9/38-29/9/38 | Calcium Gluconate | 1020 |
| | 30/9/38-8/10/38 | Digitalis | 1160 |
| | 9/10/38-11/10/38 | Salyrgan | 1540 |
| | 12/10/38-16/10/38 | Salyrgan and Parathormone | 1620 |

In this patient the administration of parathormone did not lead to any appreciable increase in salyrgan diuresis. The serum calcium estimations indicate, however, that parathormone failed to cause any increase in the concentration of calcium in the blood. Before the first injection of parathormone the serum calcium was 10.2 mgrms.%, and after the fifth it was 10.0 mgrms.%. Actually a further course of five injections was given after a lapse of four days, and the serum calcium figure was then 10.2 mgrms.%..

The next three cases demonstrate results similar to those obtained in cases K. and L.

TABLE 24

| Name | Date | Therapy | Urinary Output in c.cs. (Daily Average) | Serum Calcium mgrms.% |
|---|---|---|---|---|
| N. | 24/1/39 | S. | 1830 | |
| | 25/1/39 | S. | 1620 | |
| | 26/1/39 | S. | 1280 | |
| | 27/1/39 | S. | 1040 | |
| | 28/1/39 | S. | 1100 | |
| | 29/1/39 | S. | 1010 | |
| | 30/1/39 | S. | 1160 | |
| | 31/1/39 | S. | 1130 | |
| | 1/2/39 | S. | 840 | 10.1 |
| | 2/2/39 | S. & P. | 700 | |
| | 3/2/39 | S. & P. | 1040 | |
| | 4/2/39 | S. & P. | 1130 | |
| | 5/2/39 | S. & P. | 1250 | |
| | 6/2/39 | S. & P. | 1800 | 11.4 |
| | 7/2/39 | S. | 1860 | |
| | 8/2/39 | S. | 1510 | |
| | 9/2/39 | S. | 1330 | |
| | 10/2/39 | S. | 980 | |
| | 11/2/39 | S. | 1280 | |
| | 12/2/39 | S. | 1130 | |
| | 13/2/39 | S. | 1070 | 10.2 |

S..... Salyrgan : P..... Parathormone

The urinary output fell throughout the first period when salyrgan was given daily. The fall was arrested when parathormone was started, and the output rose again; after the fifth injection it had almost reached the original level. On stopping the parathormone but continuing the salyrgan the quantity of urine again gradually decreased. These variations in the amount of urine passed were again related to variations in the serum calcium figure as shown in the table and in Fig. 16.

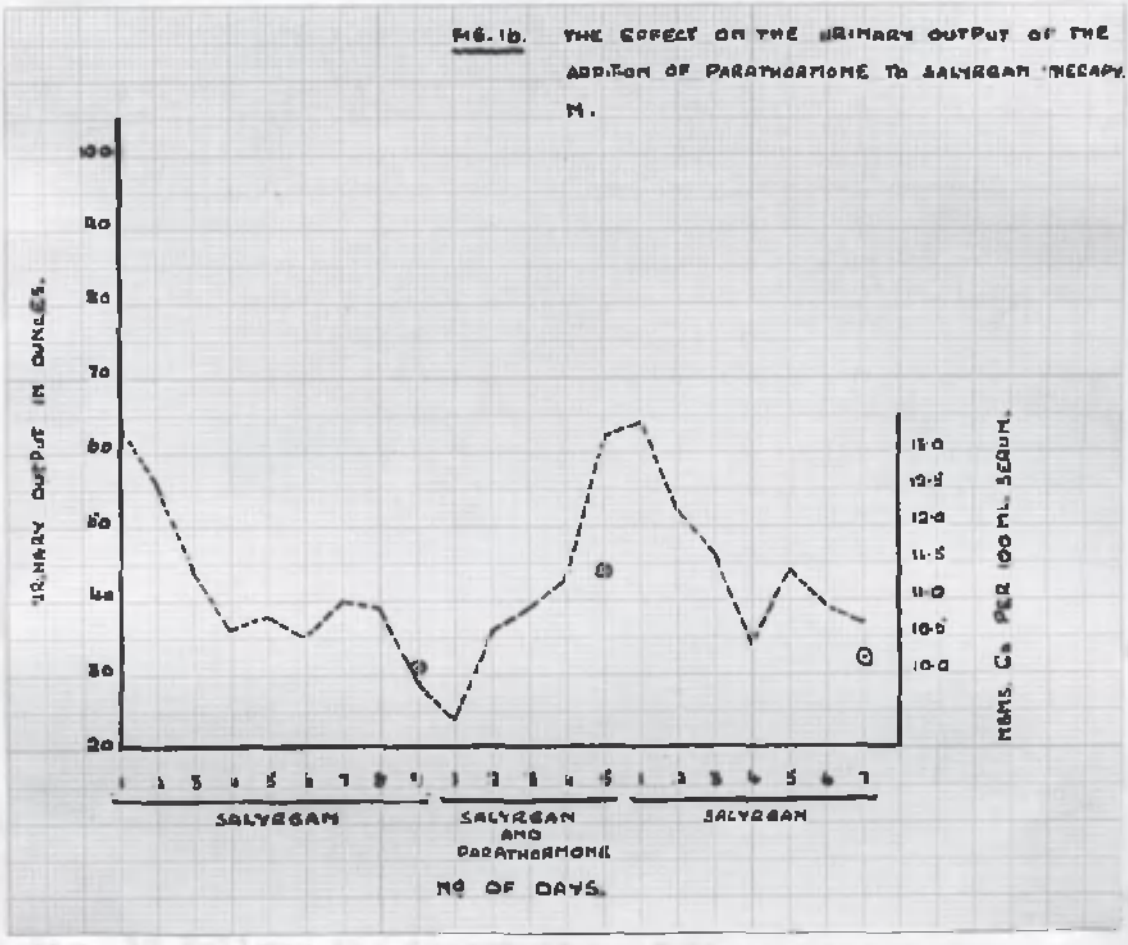



TABLE 25

| Name | Date | Therapy | Urinary Output in c.cs. (Daily Average) | Serum Calcium mgrms. % |
|---|---|---|---|---|
| O. | 17/2/39 | S. | 1300 | |
| | 18/2/39 | S. | 1070 | |
| | 19/2/39 | S. | 1160 | |
| | 20/2/39 | S. | 1160 | 10.2 |
| | 21/2/39 | S. & P. | 1160 | |
| | 22/2/39 | S. & P. | 1100 | |
| | 23/2/39 | S. & P. | 1390 | |
| | 24/2/39 | S. & P. | 1450 | |
| | 25/2/39 | S. & P. | 1680 | 11.1 |

TABLE 25 (Contd.)

| Name | Date | Therapy | Urinary Output in c.cs. (Daily Average) | Serum Calcium mgrms.% |
|---|---|---|---|---|
| | 26/2/39 | S. | 1710 | |
| | 27/2/39 | S. | 1220 | |
| | 28/2/39 | S. | 1070 | |
| | 1/3/39 | S. | 870 | |
| | 2/3/39 | S. | 840 | |
| | 3/3/39 | S. | 870 | |
| | 4/3/39 | S. | 840 | |
| | 5/3/39 | S. | 870 | |
| | 6/3/39 | S. | 930 | 10.4 |

S..... Salyrgan : P..... Parathormone

Results similar to the previous are shown in this case. Again the rise in urinary output with commencement of parathormone therapy and its fall on cessation of the parathormone were associated with rise and fall in the serum calcium. These results are shown in Fig. 17 which, with Fig. 18, follows the description of the next case.

TABLE 26

| Name | Date | Therapy | Urinary Output in c.cs. (Daily Average) | Serum Calcium mgrms.% |
|---|---|---|---|---|
| P. | 20/2/39 | S. | 1390 | |
| | 21/2/39 | S. | 1740 | |
| | 22/2/39 | S. | 1570 | |
| | 23/2/39 | S. | 1280 | |
| | 24/2/39 | S. | 1450 | |
| | 25/2/39 | S. | 1510 | |
| | 26/2/39 | S. | 1450 | 10.6 |
| | 27/2/39 | S. & P. | 1740 | |
| | 28/2/39 | S. & P. | 1740 | |
| | 1/3/39 | S. & P. | 1620 | |
| | 2/3/39 | S. & P. | 2030 | |
| | 3/3/39 | S. & P. | 1860 | 11.0 |

TABLE 26 (Contd.)

| Name | Date | Therapy | Urinary Output in c.cs. (Daily Average) | Serum Calcium mgrms.% |
|---|---|---|---|---|
| | 4/3/39 | S. | 1510 | |
| | 5/3/39 | S. | 1040 | 10.9 |
| | 6/3/39 | S. & P. | 1510 | |
| | 7/3/39 | S. & P. | 1280 | |
| | 8/3/39 | S. & P. | 1450 | |
| | 9/3/39 | S. & P. | 1830 | |
| | 10/3/39 | S. & P. | 1770 | 11.1 |
| | 11/3/39 | S. | 1310 | |
| | 12/3/39 | S. | 1160 | |
| | 13/3/39 | S. | 980 | |
| | 14/3/39 | S. | 930 | |
| | 15/3/39 | S. | 1330 | 10.7 |

S..... Salyrgan : P..... Parathormone

In this case the quantity of urine passed remained fairly constant throughout the initial course of salyrgan therapy. It was increased, however, by the addition of parathormone to the salyrgan treatment. It dropped sharply for the two days after the parathormone was stopped, but rose again to a slightly higher level than it had been in the original salyrgan period when the parathormone was restarted. It fell abruptly again when the parathormone was stopped. These changes were associated with rise and fall in the serum calcium levels, the rise corresponding to the increase in amount of urine passed and the fall to the decrease.

FIG. 17. THE EFFECT ON THE URINARY OUTPUT OF THE ADDITION OF PARATHORMONE TO SALYRGAN THERAPY.
O.

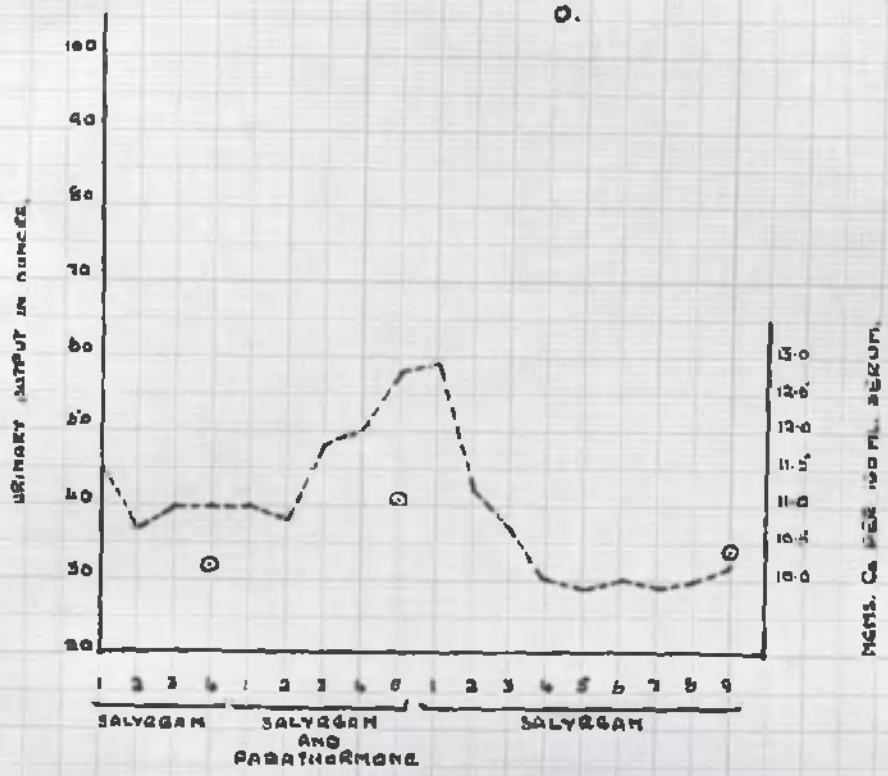
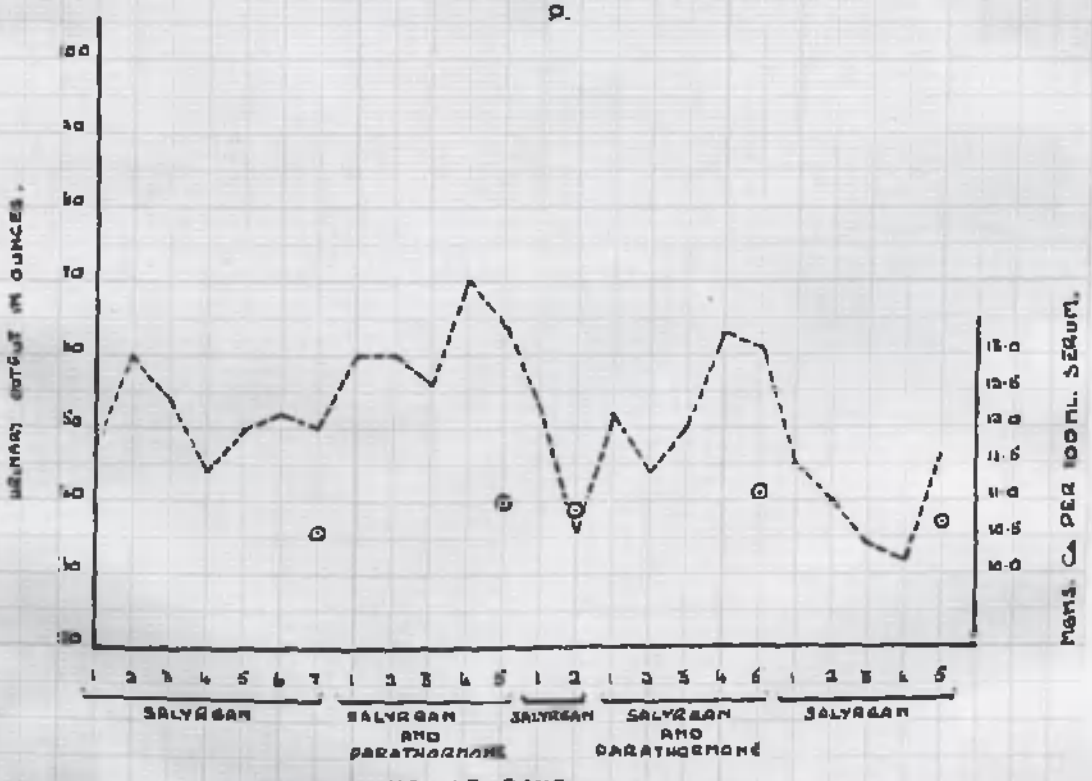



FIG. 18. THE EFFECT ON THE URINARY OUTPUT OF THE ADDITON OF PARATHORMONE TO SALYRGAN THERAPY.
O.



An examination of the results obtained from the use of parathyroid extract would indicate that it potentiates the effect of salyrgan, and that the degree of potentiation is roughly proportional to the increase in the level of serum calcium. Although in these patients the oedema was greatly reduced during parathormone treatment, there was no evidence, subjective or objective, of improvement in cardiac action. As far as could be ascertained the pulse rate, force of the pulse, and blood pressure remained unchanged. It is possible, therefore, that the parathormone acted either directly or via the increase in serum calcium on the transference of fluid from water-logged tissues to blood stream or on the renal mechanism. Calcium has the reputation of altering cellular permeability, and indeed has been used with a fair amount of success in dispelling pathological collections of fluid which have arisen from some malfunction of capillary permeability. Another point of interest is the diuretic action of ammonium and calcium chloride which is usually attributed to the fact that they tend to produce acidosis. But it must be remembered that they also lead to an increase in serum calcium. There is no evidence that parathormone produces a shift of acid-base equilibrium to the acid side and it may be suggested as a possibility that its diuretic effect is produced through the agency of a prolonged increase of serum calcium. This opens up a wide field for speculation, and although it is against the generally accepted

opinion of most workers in this field, the view may be tentatively brought forward that the rise in serum calcium has itself a diuretic effect.

Whatever the underlying cause, it would appear from the results of the present series of investigations that parathormone maintains the action of salyrgan, and prolongs and potentiates its diuretic effect.

## PART 111

## TOXICOLOGY.

Before considering the general clinical results of calcium therapy in cardiac failure some consideration must be given to the toxicity of this form of treatment.

In animals large intravenous injections of calcium salts lead to a very rapid reduction of blood pressure, inhibition of the cardiac and respiratory movements, and a rest of urinary flow. Smaller injections produce changes in the tonus of skeletal muscles. The rate of intravenous administration of calcium gluconate plays an important part in the production of untoward reactions. McGuigan and Higgins (39) stress the importance of this fact, and suggest that the administration of 10 c.cs. of a 10% solution of calcium gluconate should take at least two minutes at a constant rate. In the present series of investigations this technique was adopted with very favourable results as far as toxicity is concerned. In only one patient did serious manifestations of poisoning arise; this case will be considered in the succeeding paragraphs.

It has been shown that great similarity exists between the actions of calcium and digitalis. Whether or not digitalis sensitises the myocardium to the action of calcium or vice versa there is no doubt that an additive effect is obtained when the two drugs are given. Nyiri and Dubois (41) found that digitalis enhanced the action of calcium on the heart. A priori, therefore, it would seem right to be careful when calcium is being given to a patient whose tissues contain

digitalis. The oral administration of digitalis to a subject with hypercalcaemia is not, however, likely to be dangerous since digitalis is slow in action while calcium is rapid in producing its effect on the heart. Bower and Mengle ( 6 ) were the first to state categorically that it was dangerous to use calcium and digitalis simultaneously. An unfortunate experience with two patients led them to this conclusion. A woman, aged thirty-two, who had had m.250 of digalen was given 10 c.cs. of 10% solution of calcium gluconate because of a persistently high pulse rate (120 per minute). Two minutes after the termination of the intravenous injection, generalised convulsive movements commenced and very rapidly increased in intensity, the heart sounds disappeared and respiratory movements ceased. At the post-mortem examination nothing was found to account for this fatal issue, and it was concluded that the calcium injection was responsible. Their second patient was a man, aged fifty-five years, who, fully digitalised for heart disease, had a parathyroidectomy done because of generalised fibro-cystic osteitis. Two days after the operation a fine tremor of the hands was noted and considered to be a manifestation of tetany. He was given 10 c.cs. of a 10% solution of calcium chloride intravenously and this was followed immediately by sudden stoppage of the heart and death. Bower and Mengle thereupon investigated the problem experimentally on dogs. They found that when calcium was given to an animal who had previously received digalen, the minimum lethal dose was reduced by 60 to 70 per

cent. Previous administration of calcium to animals did not, however, reduce the minimum lethal dose of digalen.

At the commencement of the present investigation calcium was given to several patients who were receiving digitalis. No ill effect was noted until the experience which is now to be described.

The patient, a woman aged thirty years, was admitted with the manifestations of severe cardiac failure, marked dyspnoea and cyanosis and extensive oedema. The rhythm of the heart beat was irregular. There had been a long history of cardiac trouble dating from an attack of acute rheumatism in childhood. At first she was given the usual treatment - rest, appropriate diet, digitalis and mersalyl. Improvement was noted, but some cyanosis still remained and the oedema was not much reduced. The rhythm of the heart remained irregular. After a period of twenty-three days on digitalis (pulv. digitalis 6 grains daily), she was given daily intravenous injections of 10 c.cs. of 10% calcium gluconate, while digitalis therapy was continued. On March 7th, 1938, after the fourth injection of calcium gluconate, a marked fall in heart rate occurred and coupling of beats was noted. Both calcium and digitalis were stopped. Three days later, on March 10th, digitalis was recommenced only to be stopped seven days later on March 16th, owing to the appearance of many extrasystoles verified by electro-cardiograph tracings. On March 19th, digitalis was again given for two days, but again had to be stopped because of a fall in pulse rate and the reappearance of many extrasystoles.

On March 22nd, 23rd, and 24th, an intravenous injection of 10 c.cs. of 10% calcium gluconate was given once daily. Half an hour after the termination of the third injection, the patient went into a very severe rigor which lasted for forty-five minutes, vomited, and became very cyanosed. The heart rate jumped from 44 to 132 per minute. The cyanosis and tachycardia persisted until the patient died twelve hours later. Permission for post-mortem examination was not granted.

It is difficult to be absolutely certain that death was due to the administration of calcium to a subject who was saturated with digitalis. The patient was very ill on admission and throughout her period of treatment before calcium therapy was started, but the sequence of events was sufficiently dramatic to convince one of the danger of administering calcium intravenously to anyone receiving digitalis. In any case, the decision was taken not to give an intravenous injection of calcium gluconate until at least four days had elapsed since the last administration of digitalis. By such a procedure one felt that even if a patient had been receiving full doses of digitalis and was completely saturated, the saturation would have been reduced by the excretion of 8 to 9 grains of digitalis, i.e., to the extent of 35 to 40 per cent. Since this rule was complied with, no further toxic effects were encountered.

## PART IV

## CLINICAL RESULTS.

In the present section of the thesis it is proposed to attempt a clinical evaluation of the use of calcium in the therapeutics of cardiac decompensation. It is merely a platitude to remark on the difficulties of assessing the value of any form of treatment. These difficulties beset the investigator especially when he deals with cardiac failure. There are as many degrees of cardiac decompensation as there are patients, and in all there is almost always present some complicating factor such as arteriosclerosis, nephritis, or bronchitis, all of importance in modifying the efficiency of the circulation. Even a very short experience of the treatment of patients with heart failure has been enough to demonstrate the irregularity with which they respond to the same form of therapy. One patient recovers from all objective signs after a few days rest in bed, while another, although showing indications of no greater severity, fails to respond either to rest or to the administration of the digitalis glucosides. Furthermore, it is within the experience of most physicians to discover a patient who has been for long resistant to digitalis suddenly commencing to pass increased amounts of urine and quickly get rid of a large collection of oedema fluid. These points are stressed since they indicate the difficulty of coming to any conclusion in any particular case as to the precise value of some special form of therapy.

The digitalis glucosides have long been established as of the utmost value in the treatment of heart failure. No one has suggested any other drug which can compare with digitalis in efficiency. Nevertheless everyone has met with patients who have failed to respond to digitalis. In an ideal investigation one would choose for the testing out of a new drug only those subjects who, after a long course of digitalis, had remained in statu quo or even deteriorated. In the present study an attempt has been made as far as possible to choose patients who, being the subjects of advanced heart failure, had failed to react to other forms of treatment. The great disadvantage of this form of procedure is that by the time the new remedy is tried, the patient may be so ill that little can be hoped for in the way of recovery. When results had been obtained in a few cases, indicating the possibility and indeed the probability of benefit accruing from calcium therapy, it was at times very difficult to refrain from giving calcium before an adequate control period had been allowed to elapse. On occasions, indeed, a control period was dispensed with in an attempt to discover whether calcium itself had a beneficial effect quite apart from digitalis. The survey of the case histories has made one regret the omission of an adequate period of control. The only excuse which can be offered is the unknown length of control necessary for any individual subject, and the natural impatience at withholding a remedy which one believed might be of value to

the patient.

In all, calcium therapy has been given systematically to forty-one patients. This series does not include the subjects used for studying the influence of single administrations of calcium gluconate on the various manifestations of cardiac failure. Of the series of forty-one, it is believed after careful consideration of all aspects of the individual case histories that calcium therapy was of definite, and sometimes decisive, benefit in fourteen.

Criteria of Improvement.

For the purposes of a therapeutic test, it is advisable, wherever possible, to have signs rather than symptoms of betterment. On occasion, however, the patient may feel and actually be much improved, although objectively one cannot produce figures to measure the degree of recovery. Thus in fairly severe left-sided heart failure, dyspnoea may be the only indication. Sometimes even the dyspnoea may not be constant. In such a case the patient may state that he breathes much more easily, although ordinary clinical examination may not reveal a significant alteration of the rate or depth of respiration. It may be argued that this should be revealed by respiratory tracings taken with the aid of a stethograph. Recording by means of this instrument is not satisfactory unless the tracing is continuous, because with succeeding applications of the stethograph it is almost impossible to ensure the same degree of pressure on the chest wall; accordingly, the height of the wave will indicate quite

a different amplitude of breathing in each case.

It is, however, better to err on the safe side and refuse to accept evidence of improvement unless it can be measured even in a comparatively crude fashion. Otherwise there is a great temptation for patient and attendant to be enthused by the use of a new remedy, especially when it involves the paraphernalia and excitement of an intravenous injection. Accordingly, improvement has been considered to have occurred only when there has been a reduction in pulse rate, a diminution of oedema determined by repeated measurements of oedematous limbs, a reduction in the rate of breathing, or a marked lessening of cyanosis, together with subjective betterment lasting for at least three days. This period was chosen in order to make certain that the benefit obtained had some slight degree of permanence, and was not due to the excitement associated with the giving of an intravenous injection.

Before analysing the results of the series it is of advantage to consider in detail those cases which responded favourably to calcium medication; brief notes about the others are given in appendix (a).

A. Beneficial Effect obtained from Calcium after Digitalis had proved unsuccessful.

Case 1 : Mr. D.

The history in this man's case pointed to a left-sided heart failure. He complained of chronic cough and marked breathlessness on the slightest exertion.

Examination disclosed a considerable degree of dyspnoea, and a cyanotic tinge to lips, cheeks, and finger nails. There was no oedema. The heart rate was about ninety, regular in rhythm, and the sounds were faint.

He was treated by rest in bed and digitalis for five weeks. Persistence of dyspnoea and cyanosis prompted the giving of 20% glucose intravenously on 9.2.38; this was repeated on 10.2.38 and 11.2.38. His colour improved immediately after this; no change was noted in the dyspnoea. Four days after the third injection it was noticed that cyanosis was quite as marked as it had been before; accordingly, injections of 10 c.cs. of 10% calcium gluconate were started on 15.2.38. These were continued daily till 21.2.38. Progressive improvement in colour and also in the amount of exercise tolerance was thereafter noted, and he was discharged on 15.3.38, still breathless on moderate exertion, but, according to himself, able to do more than he had done for many months.

In this patient it seems permissible to attribute a considerable degree of circulatory improvement to the use of calcium gluconate. Rest in bed associated with full doses

of digitalis for five weeks did not produce any alleviation of symptoms or signs. The administration of 20% glucose led only to a very transitory betterment in cyanosis, no change being noted in the dyspnoea. Immediately after calcium gluconate injections were commenced progressive improvement in cyanosis was noted, and dyspnoea was reduced to such an extent that he was able to walk about without any discomfort. In this particular patient all the benefit that accrued from the treatment must be credited to the action of calcium on the circulation.

B. Beneficial Effect increased when Calcium preceded Digitalis Therapy.

Case 2 : Mr. B.

This man was admitted on 26.8.37 complaining of cough and shortness of breath of seven years' duration. He had had rheumatic fever twenty-two years previously.

Treatment, using calcium, was not started till 3.12.37. Thus the patient had been, for over three months, receiving the standard treatment for cardiac failure - rest in bed, appropriate diet, and digitalis in full doses, when, on December 3rd, 1937, he was found on examination to be in the position of orthopnoea, deeply cyanosed, with slight oedema of the ankles. The apex beat was in the sixth space $5\frac{1}{2}$" from the mid line. There was a loud mitral systolic murmur conducted into the axilla. The heart rate was 80 per minute and the rhythm was regular. No improvement had been noticed in his condition since his admission.

Intravenous calcium gluconate was given on 3.12.37, 6.12.37, 10.12.37, 17.12.37, and 22.12.37. He improved considerably in this time. He was much less cyanosed, and he had no attacks of cardiac asthma such as he had been having previously. No calcium was given for the next twelve days, and on 3.1.38 he took an attack of asthma. Accordingly, since it seemed that these attacks had been improved by the injections, a further 10 c.cs. of the gluconate were given. Calcium was subsequently given intravenously on 10.1.38, 24.1.38, 26.1.38, 28.1.38, 2.2.38, 16.2.38, 17.2.38, and 22.2.38.

Throughout this time the general condition improved, that is, over a period of almost three months; indeed his colour and breathing had returned sufficiently to normal for serious consideration to be given to the question of allowing him up. On 16.2.38, however, it was noticed that the heart rate had risen to 100 per minute - it had remained very steady between 70 and 80 - and on 22.2.38 it was 105 per minute with a definite setback in the patient's condition. Pulv. digitalis grain ¼ t.i.d. was given on 24.2.38, and on 3.3.38 it was reduced to grain ⅓ t.i.d., and on 11.3.38 the patient was so well that he was allowed up. Thereafter his recovery was uninterrupted and he was discharged well on 5.4.38.

This case history illustrates well both the therapeutic action of calcium itself, and also the effect which it has on subsequent digitalis treatment. Evidence is presented that calcium may have a beneficial effect on the spasmodic attacks of dyspnoea known as cardiac asthma. Only a temporary effect on the rate of the heart was produced however; lasting benefit only occurred when digitalis therapy was recommenced. It is to be emphasised that a previous course of digitalis lasting three months had done little to improve the action of the heart. Accordingly, one may conclude that calcium did something to enhance the effect of digitalis, possibly by sensitising the heart to its action. Indeed this case history tempts one to suggest that the two drugs act better in conjunction. The patient had been receiving digitalis prior to the injection

of calcium gluconate and undoubtedly there must have been a considerable amount of digitalis glucoside present in the body for some time, so that the improvement obtained from the calcium may have been due to a potentiation of the action of digitalis which was then presumably in the heart muscle.

Case 3 : Mrs. C.

This case is similar to the previous one.

The patient, a woman aged fifty years, was admitted on 3.1.38 with advanced cardiac failure. She was very dyspnoeic and markedly cyanosed, with considerable oedema affecting feet legs and thighs. There was enlargement of the heart, the apex beat being in the sixth space, 6 inches from the mid line. The rhythm was regular, and there was a loud mitral systolic murmur conducted into the axilla.

Until 24.1.38, that is for three weeks, she was given the usual treatment for such a case - rest in bed in the position of orthopnoea, sedatives, restriction of fluids, and large doses of digitalis, grain iii t.i.d. on admission and later grain ii t.i.d.

The condition was practically unchanged and on January 24th she was so ill that the prognosis was considered to be very grave. Intravenous injections of 150 c.cs. of 20% glucose were given on January 24th, 26th, and 31st. The patient remarked that she felt somewhat easier and cyanosis was noted to be rather less intense. The improvement was slight. On February 2nd an intravenous injection of 10 c.cs. of 10% calcium gluconate were given . This was repeated on the 7th, 9th, 10th, 11th, 12th, 14th, 15th, 16th, and 17th of that same month. After the first injection of calcium the breathing became easier, and there was definite reduction in the degree of cyanosis. This improvement was not, however, maintained and after the series of calcium

injections there could not be said to be any significant betterment. Thereupon digitalis therapy was recommenced with a markedly beneficial response. She was given pulv. digitalis grain $\overline{iii}$ t.i.d. on 18.2.38; the dose was reduced to grain $\dot{i}$ t.i.d. on 21.2.38, by which date the heart rate had fallen from 100 to 62 per minute. Respiratory distress was greatly relieved, cyanosis had become much less marked, and signs of oedema which had remained practically constant since admission had disappeared. The leg measurements when oedema was present and after it had disappeared are shown.

| | 28.1.38 | | 28.2.38 | |
|---|---|---|---|---|
| | Right | Left | Right | Left |
| Foot | 8 5/8 | 8 5/8 | 8 1/4 | 8 1/4 |
| Ankle | 8 3/4 | 8 3/4 | 8 1/2 | 8 1/2 |
| Leg | 12 1/2 | 13 | 11 1/2 | 11 1/2 |
| Knee | 16 | 15 1/4 | 15 | 14 3/4 |
| Thigh | 18 1/2 | 18 1/2 | 16 1/4 | 16 1/4 |

When discharged from hospital the patient had recovered from her severe illness although she was by no means fit; the lips were still slightly cyanosed, and dyspnoea on slight exertion was considerable. The size of the heart, as indicated by the position of the apex beat (now 5 1/2 inches from the mid-line), was smaller than on admission.

Here again there is evidence that digitalis used after calcium has a much more marked and beneficial effect than when used before. The reduction in the size of the heart and the improvement in respiration indicate that the function of the left side of the heart had been beneficially affected.

The fact that this resulted only after calcium administration strengthens the view that one effect of this drug is to sensitise the cardiac muscle to digitalis.

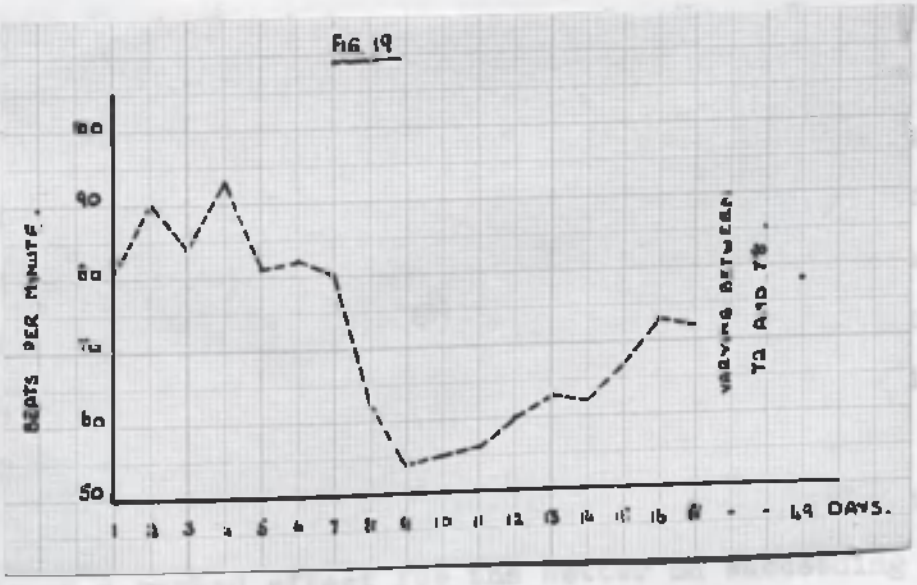
Case 4 : Mrs. A.

This patient was admitted to hospital on 22.1.38 suffering from advanced heart failure, with marked dyspnoea necessitating the position of orthopnoea, extreme cyanosis, and massive oedema. For six weeks she was treated by rest in bed, digitalis, mersalyl, and the usual dietetic measures adopted for patients with congestive heart failure. Digitalis had been given in different doses, at times very large, without any appreciable effect.

When I first saw her on March 3rd she was very ill, orthopnoeic and markedly cyanosed, and she was greatly troubled with sleeplessness. Oedema was massive and extensive, affecting the feet, legs, thighs, abdominal wall, and lumbo-sacral region; there was also marked ascites. The heart was enlarged to a marked extent, the apex beat being in the sixth space 6 inches from the mid-line. The sounds at the mitral area were replaced by systolic and diastolic murmurs, the systolic murmur being conducted into the axilla. There was auricular fibrillation, and the heart rate was 150 per minute. The oedema on 7.3.38 and at intervals throughout the subsequent period of treatment was :-

| | 7.3.38 | | 24.3.38 | | 28.4.38 | |
|---|---|---|---|---|---|---|
| | Right | Left | Right | Left | Right | Left |
| Foot | 10" | 9 1/2" | 8 5/8" | 8 1/8" | 8 1/4" | 8 1/4" |
| Ankle | 9 3/4" | 9 1/2" | 9 1/4" | 9" | 8" | 8" |
| Leg | 14" | 14 1/4" | 11 1/4" | 11 1/4" | 10 1/2" | 10 1/2" |
| Knee | 15 3/4" | 15 3/4" | 12" | 12" | 11 1/2" | 11 1/2" |
| Thigh | 17 7/8" | 17 1/2" | 15 1/4" | 15 1/4" | 13 1/4" | 13 1/2" |

Digitalis was stopped for four days. Commencing on March 7th daily injections of 10 c.cs. of 10% calcium gluconate were given. In all five doses were administered. No improvement was noted during the course of calcium therapy; the heart rate remained rapid and the clinical condition unchanged. On 12.3.38 digitalis therapy was recommenced in doses of grain $\frac{ii}{ii}$ t.i.d. - amounts which she had previously received without apparent benefit. On the evening of 12.3.38 the heart rate was 100 per minute - slower than it had been at any time since admission, that is, it had been reduced to this, its lowest level, by grain $\frac{i}{vi}$ of pulv. digitalis, and this had not been accomplished by all the digitalis of the previous weeks. It seems reasonable to associate the administration of the calcium with the marked response. The heart rate continued to fall as shown in Fig. 19.



Coincidently with the fall in heart rate, the urinary output commenced to rise with gradual lessening of the oedema. But on 24.3.38, that is, thirteen days after the last calcium injection, a most marked change occurred for the better. Within twenty-four hours oedema diminished to such a degree that the marked change was visible to the naked eye, cyanosis became much less intense, and on that day, for the first time since the illness started, the patient was able to lie flat in comfort. The marked reduction in oedema is seen from the measurements shown above taken on 24.3.38. From then on her recovery was uninterrupted, and she was discharged well on 2.5.38, by which time no trace of oedema could be detected. The final measurements when there was no evidence of oedema are shown under the date 28.4.38. The amount of digitalis given after the calcium was stopped varied, of course, depending on the degree of reaction of the patient. As has been said digitalis grain $\frac{1}{60}$ t.i.d. was commenced with. The maintenance dose was grain $\frac{1}{120}$ t.i.d.

The record of this case demonstrates once more the potentiation of digitalis action by calcium. Signs of improvement included an increased output of urine, a marked reduction of oedema, and a slowing of the pulse, none of which had occurred during the period of digitalis therapy prior to administration of calcium.

These three case histories demonstrate that calcium may exert a marked effect for the better on succeeding digitalis therapy.

C. Beneficial Effect from Calcium alone.

In the following six cases the beneficial effect of calcium must be attributed to the direct action of this substance on the heart since no digitalis had ever been given to the patient.

Case 5 : Mr. F.

The patient was a man, aged fifty-eight years, admitted on 10.12.37 with dyspnoea and oedema extending to the knees. His colour was good. There was a six months' history of progressive breathlessness. On admission the heart rate was 68 per minute. There were systolic and diastolic murmurs at the mitral area, the systolic murmur being conducted to the left axilla. The apex beat was neither visible nor palpable. The rhythm was regular.

Intravenous calcium gluconate, 10 c.cs. of the 10% solution, was given on the evening of admission and repeated daily up to and including 15.12.37, that is, six injections were given. After four the patient looked much better, felt much better, was able to lie down in bed, and the oedema had completely gone.

Case 6 : Mr. G.

This man, aged fifty-four years, had a two years' history of increasing breathlessness, and a seven weeks' history of swelling ankles. He was pale, with a cyanotic tinge of the lips. There was oedema of the legs up to the knees and a lumbar pad. The fingers were clubbed. The heart rate was 100 per minute, the heart sounds regular in rhythm, and at the mitral area there was a conducted systolic murmur.

The patient was given 10 c.cs. of 10% calcium gluconate on admission on 9.5.38, and daily thereafter up to and including 16.5.38; on 13.5.38 it was given morning and afternoon. He had, therefore, nine injections. He improved markedly. By the 16th the oedema was present only around the ankles, his colour was good and he was breathing much more comfortably. The heart rate was reduced to between 70 and 80 per minute. One week later the oedema had quite disappeared, and the patient made an uneventful recovery.

Case 7 : Mr. H.

This patient, a man aged sixty years, was admitted on 8.2.38 with massive oedema of the feet, legs, thighs, lumbar region and arms. He was pale, not cyanosed. There was surprisingly little dyspnoea. The heart rhythm was regular, the rate 75 per minute, and there were no murmurs.

An intravenous injection of 10 c.cs. of 10% calcium gluconate was given on 12.2.38, by which time no benefit had resulted from the rest in bed. This was repeated on 14.2.38, 15.2.38, 16.2.38, 17.2.38, and 21.2.38. Marked slowing of the heart rate was produced by the injections and the marked changes in the electrocardiogram in this case have already been described. (Electrocardiograms 12, Part 11, p.

By 21.2.38, improvement was most marked; oedema was practically away and this despite no great increase in diuresis. The probability is that the cardiotonic action of the calcium prevented the addition of more fluid to the oedema already present. The oedema quickly cleared entirely, the general condition improved, and the patient was discharged fit.

In this case calcium gluconate was the only drug used, and it seems reasonable to ascribe the improvement to the direct action of the calcium salt on the heart muscle.

Case 8 : Mr. I.

The patient, aged fifty-nine years, was admitted on 2.2.38. He had slight oedema of the ankles and fairly deep cyanosis of the lips. The heart rhythm was regular and the rate 82 per minute. There was a conducted mitral systolic murmur.

He was given 10 c.cs. of 10% calcium gluconate on 3.2.38, 4.2.38, 8.2.38, and 9.2.38. No other drug therapy was given. His colour was good and oedema had gone by 9.2.38. Recovery was uneventful. Heart rate remained steady between 70 and 78.

Case 9 : Mr. J.

This patient, aged forty-six years, admitted on 25.1.38, was suffering from left-sided heart failure; dyspnoea was the predominant feature, there was a bluish tinge to face and lips, and the bases of the lungs were slightly congested. There was no oedema. The heart sounds were faint, regular, and pure; the rate varied about 80 per minute. The apex impulse was 4 1/2 inches from the mid-line in the 5th space.

On 25.1.38 and again on 28.1.38 he was given 150 c.cs. of 20% glucose saline intravenously. As seemed always to be the case after intravenous glucose, there was some improvement which was, however, only temporary. On 2.2.38, in the absence of any permanent improvement, 10 c.cs. of 10% calcium gluconate were given; this was repeated on the 4th, 7th, 9th, 11th, and 14th. No further therapy was considered necessary after this date. Breathing was much improved, he was able to lie flat without dyspnoea and cyanosis had disappeared. No change was noted in the position of the apex impulse but the heart sounds became much more distinct. He was discharged well. In this case calcium proved of greater benefit than concentrated glucose and rest in bed.

Case 10 : Mrs. K.

This patient, a woman aged fifty-five years, was admitted on 25.11.37. She complained of increasing breathlessness for five years previous to admission to hospital. For the three weeks previous to her admission her legs had been swelling.

She was a very stout, very deeply cyanosed woman, necessitating the position of orthopnoea and with extensive oedema affecting feet, legs, thighs, abdominal wall and lumbar pad. The heart rhythm was regular, the rate 86 per minute. The apex impulse was in the 5th space 6 1/2 inches from the mid-line. The oedema at this time and at various stages throughout her course of treatment was as shown :-

| | 26.11.37 | | 29.11.37 | |
|---|---|---|---|---|
| | Right | Left | Right | Left |
| Foot | 9 1/2" | 9 1/2" | 9" | 9 1/4" |
| Ankle | 9 1/4" | 9 1/8" | 9 1/2" | 9 1/8" |
| Leg | 13 7/8" | 14 1/4" | 13 3/4" | 13 3/4" |
| Knee | 16 1/2" | 16 3/4" | 16 1/4" | 16 1/4" |
| Thigh | 21" | 20 3/4" | 20 1/2" | 20 1/4" |

| | 8.12.37 | | 21.12.37 | |
|---|---|---|---|---|
| Foot | 9 1/4" | 9 1/4" | 9" | 9" |
| Ankle | 8 7/8" | 9" | 8 3/4" | 8 3/4" |
| Leg | 13 1/2" | 13 1/2" | 13" | 13" |
| Knee | 16 1/4" | 16 1/4" | 16 1/4" | 16 1/4" |
| Thigh | 19 3/4" | 20" | 19 3/4" | 19 3/4" |

An intravenous injection of 10 c.cs. of 10% calcium gluconate was given on 26.11.37, and repeated on the 27th and 29th. Colour improved and she was able to lie flat. There

was slight diminution in the degree of oedema (see measurements taken on 29.12.37). Difficulty in getting into a vein through the thick layer of fat made necessary the further administration of calcium gluconate by intramuscular injection. This was done on the 6th, 7th and 8th of December when the oedema was as shown above. By this time there was the degree of improvement in oedema as shown by the above measurements, and a subjective improvement in that the colour was better and breathing was easier.

The intramuscular injections were continued daily till 14.12.37. By that time everything had cleared except for slight oedema of the feet and ankles. The colour was good. She could lie flat in bed. She felt and ate well. The heart rate was 78, and regular in rhythm.

Mersalkyl, 1 c.c. was given intravenously with good diuretic effect, so that by 21.12.37 no trace of oedema was left. Immediately the oedema was cleared in this way she was well both subjectively and objectively. It was as if the previous treatment had done everything except get rid of the last of the oedema. The final leg measurements are shown above.

In this case a very ill woman with cyanosis, dyspnoea, and oedema was carried through the whole of her illness by calcium therapy. Only 1 c.c. of salyrgan was necessary in the form of adjuvant therapy.

D. Beneficial Effect of a Second Course of Calcium Therapy.

In the next two patients the calcium sensitisation to digitalis was beautifully demonstrated by the therapeutic effect of calcium being produced on two occasions.

Case 11 : Mrs. E.

This patient was admitted on 24.2.38 with the symptoms and signs of advanced cardiac failure. She was very breathless and cyanosed with gross oedema. Treatment on the usual lines brought no improvement.

When first seen by me, on 10.3.38, she was in the position of orthopnoea, very cyanosed and oedematous. The heart rate was 96 per minute, and the rhythm regular. The oedema at this time and at intervals throughout the course of treatment is shown :-

| | 10.3.38 | | 25.3.38 | | 5.4.38 | |
|---|---|---|---|---|---|---|
| | Right | Left | Right | Left | Right | Left |
| Foot | 10" | 10 1/4" | 10" | 10 1/8" | 9 1/4" | 9" |
| Ankle | 9 1/2" | 9 3/4" | 10 1/4" | 10 1/8" | 8 1/2" | 8 3/4" |
| Leg | 15 1/2" | 15 1/4" | 14 1/4" | 14 1/3" | 11 1/2" | 11 1/2" |
| Knee | 17 1/2" | 16" | 15 1/8" | 15 3/8" | 12 1/2" | 12 1/2" |
| Thigh | 19" | 19" | 19 3/8" | 19 1/2" | 14 1/2" | 14 1/2" |

She was given 10 c.cs. of 10% calcium gluconate intravenously, digitalis having been stopped four days beforehand. The calcium was repeated on the 11th, 12th, 14th, and 15th of the month. On March 16th digitalis grain ii was recommenced and given four times per twenty-four hours. On 19.3.38, that is, four days after the digitalis had been started the heart rate was noted to be rising - it was 108

per minute. Accordingly, digitalis was stopped for four days so that calcium might be given again. On 23.3.38, 24.3.38, 25.3.38, and 26.3.38, injections of 10 c.cs. of 10% calcium gluconate were again given. Marked improvement was first noted on 25.3.38 when, in association with betterment in the colour and general condition, there was an appreciable change in the degree of oedema. Measurements taken on that date showed a diminution in the amount of oedema particularly about the leg and knee. On 27.3.38 digitalis therapy was once more commenced - in small doses of the powder, grain $\frac{1}{4}$ morning and evening - since the heart rate had been reduced to 72 per minute by the calcium itself. Five days later the dose was increased to grain $\frac{1}{4}$ t.i.d. since that seemed necessary as a maintenance dose; it was sufficient to keep the heart rate between 70 and 84 per minute. From the time digitalis was started for the second time the oedema rapidly subsided and by 5.4.38 seemed quite cleared on clinical examination. In association with subsidence of the oedema there was an improvement in the general condition and disappearance of the cyanosis. The patient was discharged well on 28.4.38.

In this case digitalis was of no avail until after the second course of calcium therapy. Unfortunately serum calcium estimations were not done so that it is impossible to say whether the ultimate response was due to a marked rise in serum calcium. The course of events, however, suggests that

in the event of failure from digitalis therapy after one period of calcium administration, it might be worth while repeating the calcium injections.

Case 12 : Mrs. M.

This patient, aged forty-five years, admitted on 18.10.37, was very ill on admission; she was cyanosed, dyspnoeic and very oedematous. There was auricular fibrillation; the heart rate was 80 per minute. The area of cardiac dullness was markedly increased both to right and left; the apex beat was in the fifth space 5 1/2 inches from the mid-line. There was a double murmur at the mitral area.

The patient was given digitalis grain $\overline{iii}$ t.i.d. and mersalyl 1 c.c. every second day in association with the other recognised forms of treatment of such cases, such as rest in bed in the position of orthopnoea, restricted fluids etc. On 29.11.37, that is, about six weeks after her admission her condition had deteriorated. Dyspnoea was more marked, as was the cyanosis. The area of cardiac dullness was a further quarter inch out to the left. Oedema was more marked; the degree of this on admission and again on November 29th was as under :-

| | 18.10.37 | | 29.11.37 | |
|---|---|---|---|---|
| | Right | Left | Right | Left |
| Foot | 9 1/2" | 10 1/2" | 10" | 10 1/2" |
| Ankle | 9 3/8" | 10 1/4" | 9 1/2" | 10 1/2" |
| Leg | 14 3/4" | 15" | 15" | 15" |
| Knee | 19" | 19" | 19" | 19" |
| Thigh | 22 1/4" | 22 1/4" | 22 1/4" | 22 1/4" |

The heart rate had risen from 80 on admission to about 180 per minute.

On this date, 29.11.37, 10 c.cs. of 10% calcium gluconate were given and repeated on 30.11.37. There was no improvement

and next day digitalis was restarted in grain $\overline{iii}$ doses at six hourly intervals. There was a rapid and marked response to digitalis on this occasion. On 2.12.37 the rate was 130 per minute, and on 3.12.37 it was 90 per minute. The patient felt and looked better than at any time since her admission. This response to digitalis following calcium must be remarked on.

Digitalis was continued in grain $\overline{ii}$ doses t.i.d., and 10 c.cs. 10% calcium gluconate given on 8.12.37, 13.12.37, 21.12.37, and 29.12.37.(At this time the inadvisability of combining digitalis and calcium therapy had not been appreciated). From this date onwards - 29.12.37 - digitalis was continued alone. The patient remained moderately well till 28.1.38 when the pulse rate was noticed to be rising again, and the patient more cyanosed and generally not so well. All medication was stopped, but since the patient got progressively worse, 10 c.cs. of 10% calcium gluconate were given on 9.2.38 and repeated on each of the following three days. No improvement was noted from the calcium injections. The patient remained ill and the heart rate rapid and irregular. But, when digitalis was recommenced on 13.2.38, a good response was again obtained. The heart rate slowed and became regular for the first time since her admission. The general condition steadily improved to a sufficient degree for the patient to be discharged well on 14.3.38.

This history may be briefly summarised. A first course

of digitalis for six weeks had no appreciable effect in ameliorating symptoms or signs. After a series of injections of calcium gluconate digitalis in the same dosage as before led to a rapid and marked response with reduction of heart rate and lessening of oedema. For two months the patient remained moderately well and then the heart rate rose, cyanosis and dyspnoea increased and the general condition rapidly deteriorated. A series of four injections of calcium gluconate produced no benefit, but on recommencing the digitalis, again rapid improvement was visible and on this occasion was maintained. This case appears to afford as satisfactory a proof as can be obtained clinically of the beneficial effect of calcium in sensitising the heart to the therapeutic action of digitalis.

E. Risk of Giving Calcium Simultaneously with Digitalis.

Occasionally when the patient has failed to respond to digitalis therapy there is a temptation to give calcium and at the same time continue with the digitalis in order to accelerate the beneficial effect of the combined treatment. This, however, is not without possible danger as the following case history shows.

Case 13 : Mr. N.

This patient, aged fifty-two years, admitted on 4.4.38, had had the right leg amputated in 1937 because of arterial embolism and gangrene. He was admitted to Stobhill Hospital suffering from embolism of the femoral artery of the left leg. Conservative treatment was employed; eventually dry gangrene developed affecting the big toe and the distal part of the second toe. The whole picture was influenced by a severe degree of myocarditis; the heart sounds were almost inaudible, the blood pressure was low - 105/80, and there was a constant cyanotic tinge to the lips. The cardiac rhythm was regular.

After the primary acute conditions had subsided and after the development of the gangrene, oedema developed affecting the foot, ankle and to a slight extent the leg up to the knee. Pulv. digitalis grain ¼ t.i.d. was being given from 2.5.38 till 3.6.38; the oedema was remaining stationary. Because of the extremely severe illness of the patient - he was lying unable to help himself, lips cyanosed, heart sounds almost inaudible - it was considered justifiable to associate calcium therapy with the digitalis. Accordingly, while the pulv. digitalis

grain ¼ t.i.d. was continued, 10 c.cs. of 10% calcium gluconate were given on 3.6.38, 4.6.38, 6.6.38, 7.6.38, and 8.6.38. No change was noticed in the oedema. There was considered to be no point in continuing the injections. The digitalis was, however, continued; on the afternoon of 9.6.38 the patient was sick and the heart rate fell by 20 beats per minute. In so far as the patient had been on digitalis for four to five weeks, prior to the administration of calcium without evidence of overaction, one must associate these features of susceptibility to the drug with the calcium. On the afternoon of 10.6.38, the oedema was noticed to be much reduced and it was quite away on 11.6.38.

The patient had been on full doses of digitalis for five weeks before calcium was given. On the day after the last of five injections of calcium, there was a sudden indication of digitalis overdosage, fortunately not of a very serious nature and accompanied by the beneficial effects of slowing of the heart rate and increase of urinary output. While not capable of offering an absolute proof, one feels convinced by the course of events that one was on the verge of a serious toxic effect produced by the joint administration of calcium and digitalis, the former producing an over-sensitisation to the latter.

F. Beneficial Action of Calcium in Patient with Irregular Heart Action.

In connection with the action of calcium on the heart rate, it has already been mentioned that it is evident chiefly in cases with regular rhythm. Therapeutically also, benefit was obtained in most part in patients with regular heart action. Nevertheless calcium may exert a beneficial effect on patients with irregular rhythm as the following case history shows.

Case 14 : Mr. L.

This man, aged fifty-two years, was admitted on 4.4.38 with signs of left- and right-sided heart failure and auricular fibrillation. He was very dyspnoeic, deeply cyanosed, and oedematous, with engorgement of the cervical veins. He was treated by the ordinary methods for six weeks - rest in bed, attention to diet, and the use of digitalis. He showed definite signs of improvement, but the heart rate remained grossly irregular. Breathing was easier and colour better. He remained improved till the end of May. Then he became again more breathless and cyanosis returned. Digitalis was stopped for four days and daily injections of 10 c.cs. of 10% calcium gluconate were given on 6.6.38, 7.6.38, 8.6.38, and 9.6.38. It was noted on 8.6.38 that the sounds were more regular, and every fourth beat was an extrasystole, the others being regular in rhythm and equal in force.

After the injection on 9.6.38, therefore, digitalis was

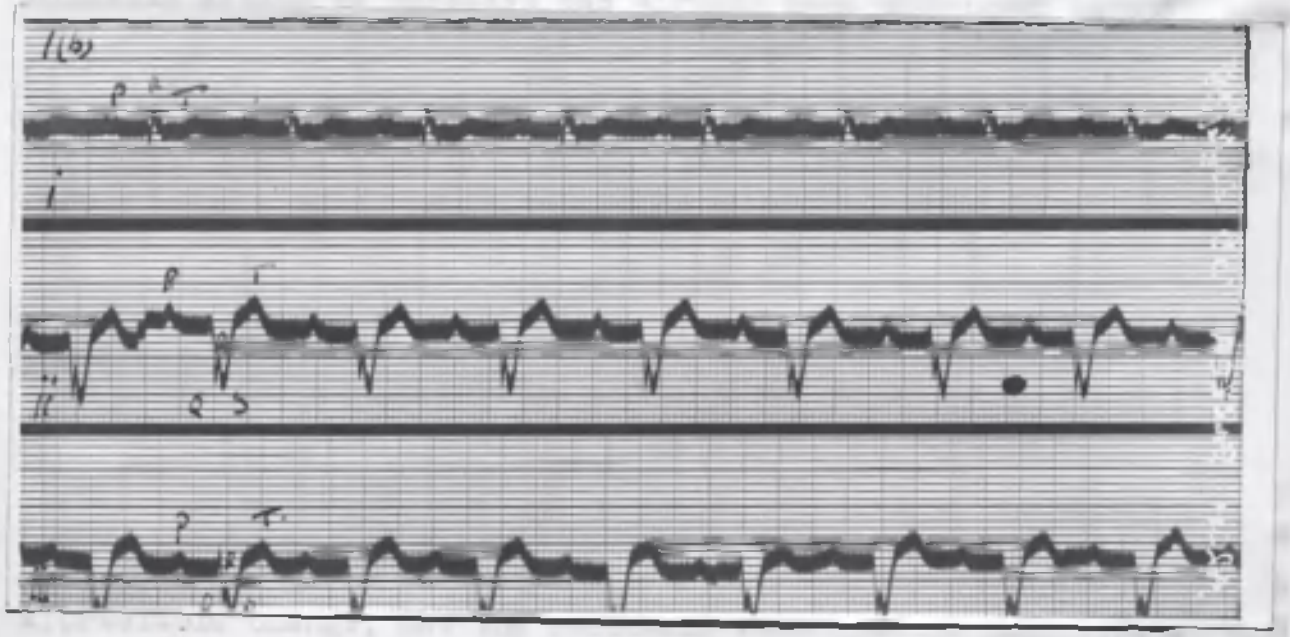
started again since it seemed likely that this would be successful now in finally re-establishing normal rhythm. He was given pulv. digitalis grain $\frac{1}{4}$ t.i.d. - a dose equal to that which he had previously received without apparent benefit. On 10.6.38, it was noted that every fifth beat was an extrasystole and an electrocardiogram was taken at this time.

He continued to improve and on 16.6.38 only occasional extrasystoles were heard. By 30.6.38 the rhythm was regular.

The course of events in the present case makes it likely that calcium had some effect in re-establishing regular rhythm. The experience obtained during the present work points to the relative inefficiency of calcium in the treatment

of patients with irregular rhythm. The case history just detailed suggests that the use of calcium should be considered in such patients when they have failed to react to digitalis therapy.

The electrocardiogram taken when regular rhythm had been established is shown below.



Showing Favourable Response to Parathyroid Hormone.

Before reviewing the clinical results, I should like to describe one case in which parathyroid extract appeared to be of benefit in the treatment of cardiac decompensation.

The value of parathyroid extract in potentiating the diuretic action of mersalyl has already been discussed in a previous section. Its use, however, is clearly worth considering as a general therapeutic measure in cardiac failure even when there is no oedema. The hypercalcaemia produced by the extract should be of value in augmenting the digitalis effect. Unfortunately parathyroid hormone is expensive so that one had to limit its use to a few patients who, while not responding to ordinary treatment, seemed likely to benefit by an induced hypercalcaemia. Three patients were given parathyroid therapy. Two showed no appreciable change, but the following case history demonstrates the benficial results which may ensue from this form of therapy.

Miss H.B.

The patient, a woman aged seventy years, was admitted on 11.5.38. She was very ill; dyspnoea was marked, the face and lips were cyanosed, and slight oedema was evident round the ankles. The cardiac rhythm was irregular, and the heart rate varying between 90 and 100 per minute. There was an absence of response to treatment with digitalis, euphyllin, etc. Indeed the patient became progressively worse. A note in the case-sheet on 26.5.38 stated - "Much weaker: pulse irregular and weak".

The heart rate remained about 90 per minute.

An intravenous injection of 10 c.cs. of 10% calcium gluconate was given on 27.5.38. This was repeated on 28.5.38, 29.5.38, 30.5.38, and 31.5.38. There was no gross change in the condition. Parathormone 1 c.c. intramuscularly daily was started on 1.6.38. After the third injection the patient was noted to be definitely better. On 6.6.38 the case-history states - "The patient has improved greatly since commencement of parathyroid therapy. She is sitting up and taking an interest and the previous torpor has gone". On this date the rhythm was regular and the heart rate 76 per minute. Parathormone was stopped on 11.6.38 when the signs had all cleared except for some oedema. Subsequent recovery was uneventful.

## Summary of the Results of the Administration of Calcium in Cardiac Decompensation

The effect of the intravenous administration of 10 c.cs. of 10% calcium gluconate to the forty-one patients whose response to treatment is detailed in Part IV and Appendix (a) is summarised in the following table.

TABLE 27

Effect of Calcium Therapy on Cardiac Decompensation.

| | Rhythm Regular | | Rhythm Irregular | |
|---|---|---|---|---|
| | Total | Improved | Total | Improved |
| Previously on digitalis | 6 | 5 | 12 | 3 |
| Not previously on digitalis | 10 | 6 | 13 | 0 |
| Both groups | 16 | 11 | 25 | 3 |

As has already been stated it is extremely difficult to determine whether any particular form of treatment is responsible for a successful issue in any one patient. Nevertheless, the data obtained in the present investigation and summarised in Table 27 are sufficiently impressive to warrant the serious consideration of intravenous calcium therapy in cardiac failure which has not responded to the administration of digitalis. This is specially the case when the heart rhythm is regular. In six patients with

regular rhythm at least one may say that the investigation was as adequately controlled as is possible in clinical work. Of these six patients no fewer than five showed definite evidence of improvement. Of the group of ten not previously receiving digitalis six responded favourably to calcium therapy. It is probable that these six would have reacted equally well to digitalis, and the most that can be claimed for calcium in this group is that it probably had a therapeutic action. The results are quite different in patients with irregular heart rhythm. Here, of twenty-five patients receiving calcium therapy, only three improved. These three, however, were well controlled, and it is considered justifiable to associate the administration of the calcium with the recovery in each case.

As a result of the present investigation the following conclusions may be drawn. Intravenous calcium gluconate in doses of 10 c.cs. of the 10% preparation is indicated in those cases where there has been failure to respond to digitalis. This is specially the case when the heart rhythm is regular. The digitalis should be stopped for three to four days before the calcium is given to ensure that the body is not saturated with digitalis, since the addition of calcium in this state may lead to serious results. The injections should be given daily, or in urgent cases twice daily for four to six days (i.e. on an average five to six injections), and then digitalis started again immediately. In this way the digitalis action is much enhanced in a considerable

number of cases, and seemingly hopeless cases may be improved, sometimes to a very considerable extent. The whole procedure should be repeated if there is no reaction from the one series of injections since it has been found that there may be a beneficial effect from a second.

## GENERAL SUMMARY

Part I. An account is given of the previous work on the action of calcium on the heart and peripheral circulation, with special reference to patients suffering from cardiac failure.

Part II. The scope of the present work is described.

(a) In patients with heart failure the values for serum calcium concentration showed greater variation than in a "control" series without cardiac involvement. In a few cases where estimations were made shortly before death, the values for serum calcium were either above or below the normal limits. Digitalis therapy produced in many patients an increase in the concentration of serum calcium. These results suggest that calcium in some instances plays a part in the compensation of the failing heart.

(b) Calcium was found to slow the heart rate, the rhythm playing a most important part in the degree of slowing produced. When the rhythm was regular the induced bradycardia was much greater, and the percentage fall in rate was roughly proportional to the original rate.

(c) Serial electrocardiogram tracings revealed a high incidence of sinus slowing after the calcium injection.

(d) Previous atropinisation prevented, in ten out of fifteen cases, the onset of "calcium" bradycardia. This, together with the electrocardiograph findings and the greater response when the rhythm is regular, suggests that the fall in heart rate is in large measure due to stimulation of the vagal

mechanism.

(e) The results obtained in the investigation of the action of calcium upon the blood pressure did little to clear up the dubiety which exists in this connection. It would appear that elevation and lowering of the pressure are equally liable to be produced, but there is a rather higher incidence of elevation than of lowering of the pulse pressure.

(f) The venous pressure, measured by the column of blood in the jugular vein, is reduced after the injection of calcium gluconate.

(g) Blood viscosity is increased in congestive heart failure without oedema. Intravenous administration of calcium gluconate led to a reduction in viscosity in patients with cardiac decompensation, but no change in healthy subjects.

(h) The respiratory rate is reduced by the injection of calcium, and the respirations may be made more regular.

(i) The effect of calcium gluconate on diuresis was studied. Single or repeated intravenous injections had little if any influence on urinary volume, but potentiated the diuretic action of digitalis given later. Parathyroid hormone was used to produce an elevation of serum calcium; when this was successful a marked potentiation of mersalyl diuresis was produced.

Part III. The dangers of intravenous calcium therapy are discussed. A typical case is described, and a method of useage in association with digitalis is suggested. Given slowly and regularly the injection of calcium gluconate is a safe procedure.

Part IV. Details are given here and in Appendix (a) of the clinical results of the administration of calcium gluconate to forty-one patients with advanced heart failure, many of whom had failed to respond to other forms of treatment including digitalis. Fourteen appeared to benefit from calcium therapy. Regularity of heart rhythm appeared to be favourable to the successful action of calcium although in three instances improvement was noted in the presence of auricular fibrillation. Based on these findings the suggestion is made that intravenous calcium therapy should be adopted for patients with cardiac decompensation who have not responded to the exhibition of digitalis.

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## APPENDIX

### (a) Brief Clinical Notes on Cases not Described in Part IV.

The other twenty-seven patients not described in Part IV who were treated by the intravenous administration of calcium gluconate at some time during their illness either failed to respond satisfactorily, or did not show objective signs sufficiently marked for conclusions to be drawn. The treatment afforded them is given briefly for the sake of completeness.

Mrs. G.A., aged seventy-two years.

Admitted : 6.1.38.

Complaint : Praecordial pain shooting down to the epigastrium and through to the back. Four years' history. Breathlessness for several years, severe only lately.

Examination : Colour good. No dyspnoea or oedema. Heart rate 92 per minute; rhythm regular. Mitral systolic murmur, conducted into the left axilla. Sounds faint. Cardiac dullness within normal limits.

Treatment :

6.1.38 : 150 c.cs. of 20% glucose intravenously.
14.1.38 : 150 c.cs. of 40% glucose intravenously.
26.1.38 : Allowed up. No pain for one week.
28.1.38 : Recurrence of pain in chest.
29.1.38 : 10 c.cs. of 10% calcium gluconate intravenously.
30.1.38 : 10 c.cs. of 10% calcium gluconate intravenously.
31.1.38 : 10 c.cs. of 10% calcium gluconate intravenously.
4.2.38 : Allowed up and remained well. No further pain until discharge on 22.2.38.

Mr. W.B., aaged fifty-two years.

Admitted : 10.3.38.

Complaint : Breathlessness and tightness in the chest of three months' duration.

Examination : Slight cyanosis. No marked dyspnoea. Oedema of feet, ankles, and lumbar region. Heart rate about 150 per minute; auricular fibrillation.

Treatment :

11.3.38 : 10 c.cs. of 10% calcium gluconate intravenously.
12.3.38 : 10 c.cs. of 10% calcium gluconate intravenously.
14.3.38 : 10 c.cs. of 10% calcium gluconate intravenously.

There was no response, either subjectively or in the fibrillation. The patient responded to digitalis.

Mrs. A.C., aged sixty-nine years.

Admitted : 2.4.38.

Patient was semi-comatose and unable to give any history. She could not swallow digitalis. Oedema was so gross that the arms could not be used for intravenous injections.

Treatment :

2.4.38 : 10 c.cs. of 10% calcium gluconate intramuscularly.
4.4.38 : 10 c.cs. of 10% calcium gluconate intramuscularly.
5.4.38 : 10 c.cs. of 10% calcium gluconate intramuscularly (twice).
6.4.38 : 10 c.cs. of 10% calcium gluconate intramuscularly (twice).
7.4.38 : 10 c.cs. of 10% calcium gluconate intramuscularly (twice).
8.4.38 : 10 c.cs. of 10% calcium gluconate intramuscularly (three times).

There was no response to treatment, the patient remaining seriously ill until 9.4.38 when she died.

Mr. J.C., aged sixty-four years.

Admitted : 10.2.38.

Complaint : Breathlessness of increasing severity throughout the previous year.

Examination : Highly-coloured man. No cyanosis. No oedema. Dyspnoea the most notable feature. Heart sounds good; rhythm regular.

Treatment :

16.2.38 : 10 c.cs. of 10% calcium gluconate intravenously.
16.2.38 : 10 c.cs. of 10% calcium gluconate intravenously.

No more calcium was given because of a marked increase in the number of red blood cells. This jumped from 5,000,000 per c.mm. to figures varying from 9-11,000,000 per c.mm., and was associated with a marked increase in the blood viscosity. Both the viscosity and the number of red cells fell gradually after the cessation of the injections, but they were still considerably above normal when the patient went out on his own responsibility ten days after the last injection.

Mrs. T.C., aged forty-one years.

Admitted : 21.3.38.

Complaint : Breathlessness increasing in severity. Occasional praecordial pain and palpitation.

Examination : Patient not gravely ill. Slight cyanosis. No marked dyspnoea. No oedema. Auricular fibrillation; heart rate 90 per minute.

Treatment :

Injections of 10 c.cs. of 10% calcium gluconate were given on five successive days from 22.3.38 without affecting the fibrillation or the general condition of the patient. The cyanosis persisted and that the fibrillation was still present also was verified by the electrocardiogram.

Mrs. R.C., aged forty-four years.

Admitted : 26.4.38.

Complaint : Extreme breathlessness of some months' duration and swelling of the legs for some weeks back.

Examination : Patient was very ill on admission. Oedema very extensive, affecting feet, legs, lumbar region, and left arm. Cyanosis marked. Breathlessness demanding the position of orthopnoea. Auricular fibrillation; heart rate 120 per minute.

Treatment :

The ordinary routine treatment - digitalis, salyrgan, etc. - was given without beneficial response until 1.5.38 when the digitalis was stopped and calcium therapy started after four days. Because of the oedema of the arms calcium gluconate was given intramuscularly. It was given twice on 5.5.38 and three times on 9.5.38. On 10.5.38 10 c.cs. of 20% calcium gluconate were given, and then digitalis recommenced in large doses but without benefit, the patient dying on 15.5.38.

Mrs. C.C., aged forty-eight years.

Admitted 8.3.38.

Complaint : Marked breathlessness and swelling of ankles of several months' duration.

Examination : Patient very ill on admission. Marked cyanosis. Extensive oedema. Auricular fibrillation; heart rate about 150 per minute.

Treatment :

There was no response to the usual methods of treatment - digitalis etc. - till 21.3.38. An intravenous injection of 10 c.cs. of 10% calcium gluconate was given on 25.3.38, 26.3.38, and 27.3.38, and digitalis then restarted. The heart rate then fell gradually to 84 per minute - it had not been less than 110 per minute previously - but the fibrillation persisted, and the general condition gradually worsened until 7.4.38 when the patient died.

Mr. J.C., aged fifty-four years.

Admitted : 24.2.38.

Complaint : Cough and breathlessness of many years' duration.

Examination : Chronic bronchitis severe. Marked cyanosis. Breathlessness demanding the position of orthopnoea. Marked increase in cardiac dullness. Heart sounds inaudible. Rhythm of pulse irregular.

Treatment :

24.2.38 : 10 c.cs. of 10% calcium gluconate intravenously.

25.2.38 : 10 c.cs. of 10% calcium gluconate intravenously.

26.2.38 : 10 c.cs. of 10% calcium gluconate intravenously.

The patient improved symptomatically, and the heart sounds became faintly audible. After talking normally to his visitors on 26.2.38, he suddenly collapsed and died.

Mrs. J.E., aged fifty-nine years.

Admitted : 23.5.38.

Patient unable to give history.

Examination : Patient very ill on admission. Extensive oedema. Marked cyanosis. Mental confusion. Cardiac rhythm irregular.

Treatment :

Digitalis etc. was given till 29.5.38 with gradual deterioration in the patient's condition. The digitalis was then stopped and calcium therapy started after a lapse of four days. An intravenous injection of 10 c.cs. of 10% calcium gluconate was given on 2.6.38, 3.6.38, 4.6.38, 6.6.38, and 7.6.38. There was no gross change in the patient's condition throughout this period. Digitalis was then recommenced in large doses. The heart rate fell, but the general condition did not improve until she left hospital against advice on 16.6.38.

Mr. H.F., aged forty-eight years.

Admitted : 25.2.38.

Complaint : Cough and breathlessness on exertion for many years.

Examination : Marked chronic bronchitis. Slight cyanosis. Slight dyspnoea. Heart rate 90 per minute; rhythm regular.

Treatment :

An intravenous injection of 10 c.cs. of 10% calcium gluconate was given daily from 25.2.38 until 2.3.38 inclusive. The heart rate fell to 75 per minute and remained more steady, but there was no change in the symptoms or signs.

Mr. H.H., aged fifty-eight years.

Admitted : 8.2.38.

Patient unable to give history.

Examination : Patient very ill on admission. Marked cyanosis. Extreme dyspnoea. Heart sounds inaudible.

Treatment :

Failure to respond to digitalis therapy prompted the giving of 10 c.cs. of 10% calcium gluconate intravenously on 25.2.38, 26.2.38, 28.2.38, and 1.3.38. There was no beneficial response to the calcium therapy, nor did a repeat course of digitalis produce any improvement.

Mr. A.K., aged sixty-four years.

Admitted 3.2.38.

Complaint : Cough and breathlessness of several years' duration.

Examination : Definite chronic bronchitis with slight cardiac failure. Dyspnoea fairly severe. Slight cyanosis. Cardiac rhythm irregular.

Treatment :

10 c.cs. of 10% calcium gluconate were given intravenously on 4.2.38, 7.2.38, and 9.2.38 without any marked change in the patient's condition. Digitalis was then given, but it did not produce any improvement either, the patient remaining dyspnoeic and slightly cyanosed, and the cardiac rhythm remaining irregular.

Mr. J.L., aged fifty-one years.

Admitted : 3.5.38.

Complaint : Severe breathlessness for many months; swelling of feet and legs for past three months.

Examination : Patient very ill on admission. Extensive oedema. Marked cyanosis. Extreme dyspnoea, necessitating position of orthopnoea. Cardiac rhythm irregular; heart rate about 115 per minute.

Treatment :

Digitalis etc., without improvement, until 23.5.38. An intravenous injection of 10 c.cs. of 10% calcium gluconate was given on 27.5.38 and daily until 1.6.38. Digitalis was then recommenced, but there was an absence of response to any form of therapy.

Mr. W.M., aged twenty-six years.

Admitted : 3.1.38.

Complaint : Breathlessness and swelling of ankles of some years' duration.

Examination : Patient very ill. Very extensive oedema. Marked cyanosis. Severe dyspnoea demanding position of orthopnoea. Mental confusion. Cardiac rhythm irregular.

Treatment :

Digitalis etc. was given until 29.1.38 by which time the patient's condition had still further deteriorated. Accordingly an intravenous injection of 150 c.cs. of 20% glucose was given on 1.2.38. There was a transitory improvement which was not, however, maintained on the following day. An intravenous injection of 10 c.cs. of 10% calcium gluconate was therefore given on 2.2.38; this was repeated on 8.2.38 and 9.2.38. There was no improvement from any form of therapy. The patient died before digitalis therapy could be recommenced.

Mr. H.M., aged forty-two years.

Admitted : 17.2.38.

Complaint : Breathlessness on slight exertion.

Examination : There were few signs of cardiac failure except a very rapid heart rate of 153 per minute associated with an irregular rhythm. There was slight dyspnoea, but the colour was good and there was no oedema.

Treatment :

An intravenous injection of 10 c.cs. of 10% calcium gluconate was given on 18.2.38, 19.2.38, 21.2.38, 22.2.38, and 23.2.38. The heart rate dropped to about 110 per minute, but on 24.2.38 the patient developed pneumonia from which he died.

Mr. P. McC., aged fifty-four years.

Admitted : 14.2.38.

Patient unable to give any history.

Examination : Patient very ill on admission. Severe dyspnoea. Marked cyanosis, and extensive oedema. Gross cardiac enlargement both to the right and left. Heart rhythm irregular.

Treatment :

Digitalis was vomited several times immediately after it was given on the day of admission. Calcium gluconate was therefore given intravenously on 15.2.38, 16.2.38, 17.2.38, 18.2.38, and 19.2.38. On 21.2.38, 100 c.cs. of 30% glucose were given intravenously in the absence of beneficial results. Large doses of digitalis were given and retained from 23.2.38. A deterioration of the condition was evident on 25.2.38. Venesection was performed but without avail, the patient dying on that date.

Miss A. McC.,

This is the case which has been fully described in the section dealing with toxicology.

Mrs. J.R., aged seventy-three years.

Admitted : 6.2.38.

Complaint : Breathlessness on the slightest exertion.

Examination : The patient was a stout plethoric woman. The blood pressure was high - 210/140. There was some cyanosis, and exercise tolerance was poor. There was auricular fibrillation, and the heart rate was 130 per minute.

Treatment :

An intravenous injection of 10 c.cs. of 10% calcium gluconate was given on 7.2.38, 9.2.38, and 11.2.38. By this time the patient felt and looked better, but the heart rate was still about 105 per minute, and the rhythm remained irregular. She remained in this state without further treatment until 7.3.38 when the heart rate started to rise again, and on the night of 7.3.38 the patient had an attack of cardiac asthma. Accordingly the calcium injection was repeated on 8.3.38, 9.3.38, 10.3.38, 11.3.38, and 12.3.38. She had again improved by this time, but, on the injections being stopped, she relapsed again on 16.3.38. Digitalis was then given with good effect. The response was immediate, only 45 minims of tincture of digitalis being required to lower the rate to 86 per minute with associated clinical improvement. The very small amount of digitalis required for the beneficial result may have been associated with the previous calcium therapy,

Mr. S.S., aged fifty-nine years.

Admitted : 26.12.37.

Patient unable to give any history.

Examination : Patient very ill on admission. Mentally confused. Marked cyanosis. Extreme dyspnoea. Extensive oedema. Auricular fibrillation; heart rate 112 per minute.

Treatment :

Ordinary routine treatment including the exhibition of digitalis in full doses was carried out until 27.1.38, when, in the absence of improvement, 150 c.cs. of 20% glucose were given intravenously. A slight improvement was noted the next day, but this was not maintained. On 31.1.38, 1.2.38, and 2.2.38, 10 c.cs. of 10% calcium gluconate were given intravenously, but the patient's condition deteriorated still further and he died on 2.2.38.

Mr. L.W., aged fifty-three years.

Admitted : 7.5.38.

Complaint : Increasing breathlessness and swelling of legs for some months past.

Examination : Patient very ill on admission. Marked dyspnoea necessitating position of orthopnoea. Extreme pallor. Extensive oedema. Cardiac rhythm regular.

Treatment :

Ordinary routine treatment including digitalis was given until 30.5.38. In the absence of beneficial response calcium therapy was commenced on 3.6.38. An intravenous injection of 10 c.cs. of 10% calcium gluconate was given on the 3rd, 4th, 6th, 7th, 8th, and 9th of the month. Digitalis was then recommenced on the 9th in doses equal to that which had been given before the calcium therapy. On the evening of the 10th the heart rate was 70 per minute - the slowest it had been at any time since admission to hospital. On the next day, however, "coupling" was noted and the digitalis had to be stopped. Twenty-six grains of the powdered leaf had produced "coupling" after calcium therapy, although this had never been noted before the calcium injections when digitalis had been given in full dosage for almost four weeks. Although the digitalis was restarted after the "coupling" had stopped, this patient became progressively worse and died.

Mr. P.R., aged sixty years.

Admitted : 10.1.38.

Complaint : Swelling of legs for some months back.

Examination : Stout, plethoric man, with fairly marked cyanosis. Extensive oedema. Heart rate irregular, about 105 per minute.

Treatment : An intravenous injection of 150 c.cs. of 20% glucose was given on 11.1.38 and 10 c.cs. of 10% calcium gluconate on 12.1.38, and 14.1.38. In the absence of beneficial response digitalis was commenced with good results.

Mrs. E. McW., aged fifty-eight years.

Admitted : 3.12.37.

Complaint : Cough and breathlessness of many years' standing.

Examination : Patient very ill on admission. Cyanosis very marked. No oedema. Both lungs showed evidence of marked bronchitis. Heart enlarged to the left. Cardiac rhythm regular.

Treatment :

The patient was unable to swallow digitalis, either in the powder or liquid form. She was accordingly given 10 c.cs. of 10% calcium gluconate intravenously on 3.12.37 and 4.12.37, but she died without showing any change in the condition on 5.12.37.

Mrs. D.N., aged forty-four years.

Admitted : 5.12.37.

Complaint : Severe breathlessness for some years, and swelling of ankles of two months' duration.

Examination : Dyspnoea demanding the position of orthopnoea. Marked cyanosis. Extensive oedema. Marked cardiac enlargement; apex impulse in sixth space 6 inches from mid-line. Cardiac rhythm irregular.

Treatment :

An intravenous injection of 10 c.cs. of 10% calcium gluconate was given on 6.12.37, 7.12.37, 10.12.37, and 11.12.37 with good response. Colour improved and breathing was much easier. There was gradual progressive improvement until 20.12.37 when the patient suddenly collapsed and died.

Mr. J.K., aged thirty years.

Admitted : 17.3.37.

Complaint : Praecordial pain, palpitation, and breathlessness, dating from an attack of rheumatic fever ten years previously.

Examination : Fairly marked cyanosis. Severe dyspnoea. No oedema. Mitral systolic murmur conducted into the left axilla. Moderate cardiac enlargement.

Treatment :

Ordinary routine treatment, including digitalis therapy, was carried out for eight months from the time of admission. No benefit resulted. Accordingly an intravenous injection of 10 c.cs. of 10% calcium gluconate was given on 22.11.37 and on six successive days thereafter. The patient showed marked improvement in colour and the breathing became easier during the course of injections, but the fibrillation and oedema persisted. Digitalis was recommenced after the series of calcium injections without any further noticeable benefit to the patient. He went out against advice one week after digitalis treatment had been recommenced.

Mr. J.M., aged sixty years.

Admitted : 3.11.37.

Complaint : Breathlessness for the previous two months.

Examination : Patient not seriously ill. Some dyspnoea, and slight cyanosis of face and lips. Slow fibrillation; heart rate 74 per minute.

Treatment :

An intravenous injection of 10 c.cs. of 10% calcium gluconate was given daily for four days from 4.11.37 with no apparent benefit resulting to the patient. The fibrillation was controlled, and the breathing made easier and colour improved by digitalis given subsequently.

Mrs. J.W., aged fifty-seven years.

Admitted : 2.12.37.

Complaint : Breathlessness for the previous year, increasing in severity lately.

Examination : Marked cyanosis. Fairly severe dyspnoea. No oedema. Cardiac rhythm irregular; heart rate about 120 per minute.

Treatment :

The patient was sick, on the day of admission, on several occasions just after the administration of digitalis. Accordingly 10 c.cs. of 10% calcium gluconate were given on 3.12.37 and daily for the five succeeding days. No gross change was noted in the patient's condition. Digitalis was again given but was again vomited.
The condition became rapidly worse, and the patient died despite venesection and oxygen administration.

Mrs. W.S., aged thirty-seven years.

Admitted : 4.6.37.

Complaint : Breathlessness and swelling of legs of several months' duration.

Examination : This patient had been in and out of hospital for eight years previously with heart disease dating from an attack of rheumatic fever in childhood. There was extensive oedema and ascites. Cyanosis was marked, and there was severe dyspnoea. The cardiac rhythm was irregular.

Treatment :

The patient was mentally confused on the evening of admission, and also on the following day, and refused to swallow medicine. Accordingly 10 c.cs. of 10% calcium gluconate were given intravenously once on the evening of admission and twice on the following day. There was no gross change in the condition. The next day, however, the patient was more rational, and took digitalis by mouth. The response to digitalis was good and recovery, to as great a degree as could be expected in her case, was uneventful.

(b)

## TABLE 28

Serial Blood Viscosity Estimations in Thirty-Five Patients under Treatment for Heart Failure to Show the Relationship of the Viscosity to the Degree of Oedema and Cyanosis.

| Name | Date | Oedema | Cyanosis | Viscosity |
|---|---|---|---|---|
| A. | 2/3/38 | +++ | + | 4.8 |
| | 14/3/38 | ++ | + | 5.1 |
| | 24/3/38 | + | + | 5.7 |
| | 29/3/38 | - | + | 5.6 |
| | 28/4/38 | - | - | 5.1 |
| B. | 6/1/38 | - | ++ | 5.4 |
| | 14/1/38 | | + | 5.2 |
| | 25/1/38 | | - | 4.9 |
| C. | 11/3/38 | +++ | ++ | 4.8 |
| | 15/3/38 | ++ | ++ | 5.5 |
| | 24/3/38 | + | + | 7.2 |
| | 29/3/38 | - | - | 5.5 |
| D. | 22/12/37 | - | +++ | 6.8 |
| | 26/1/38 | | +++ | 7.7 |
| | 2/2/38 | | + | 5.3 |
| | 16/2/38 | | + | 5.6 |
| | 5/4/38 | | - | 5.7 |
| E. | 12/1/38 | ++ | +++ | 7.3 |
| | 25/1/38 | + | ++ | 7.6 |
| | 2/2/38 | + | ++ | 8.0 |
| | 7/2/38 | + | + | 7.2 |
| | 10/3/38 | + | ++ | 8.4 |
| F. | 4/4/38 | +++ | + | 4.9 |
| | 5/4/38 | ++ | + | 5.3 |
| | 6/4/38 | ++ | + | 4.9 |
| | 7/4/38 | ++ | + | 4.3 |
| | 8/4/38 | ++ | + | 4.9 |
| G. | 5/1/38 | - | + | 5.4 |
| | 21/3/38 | + | + | 4.5 |
| | 24/3/38 | + | + | 4.5 |
| | 30/3/38 | + | + | 4.3 |
| | 4/4/38 | + | + | 4.6 |
| | 5/4/38 | + | ++ | 5.3 |

TABLE 28 (contd.)

| Name | Date | Oedema | Cyanosis | Viscosity |
|---|---|---|---|---|
| H. | 16/2/38 | - | + | 9.1 |
| | 17/2/38 | | ++ | 12.4 |
| | 18/2/38 | | ++ | 11.0 |
| | 19/2/38 | | ++ | 11.2 |
| | 21/2/38 | | ++ | 11.0 |
| | 22/2/38 | | ++ | 12.4 |
| | 23/2/38 | | ++ | 10.5 |
| | 24/2/38 | | ++ | 10.4 |
| | 25/2/38 | | + | 8.8 |
| | 26/2/38 | | + | 8.8 |
| | 28/2/38 | | + | 9.0 |
| I. | 28/3/38 | - | ++ | 6.8 |
| | 30/3/38 | | - | 5.2 |
| | 31/3/38 | | - | 5.7 |
| J. | 15/12/37 | - | ++ | 6.5 |
| | 9/2/38 | | +++ | 9.2 |
| | 10/2/38 | | ++ | 6.4 |
| | 11/2/38 | | ++ | 7.8 |
| | 12/2/38 | | + | 6.8 |
| | 16/2/38 | | + | 7.6 |
| | 10/3/38 | | - | 5.9 |
| K. | 25/3/38 | - | ++ | 6.8 |
| | 5/4/38 | | + | 7.8 |
| L. | 18/3/38 | - | +++ | 6.0 |
| | 20/3/38 | | + | 5.4 |
| M. | 25/2/38 | - | +++ | 6.2 |
| | 2/3/38 | | ++ | 5.7 |
| N. | 2/3/38 | ++ | ++ | 5.4 |
| | 14/3/38 | ++ | ++ | 5.2 |
| | 24/3/38 | ++ | ++ | 5.6 |
| | 25/3/38 | + | + | 5.4 |
| | 26/3/38 | + | + | 5.3 |
| | 28/3/38 | - | - | 5.0 |
| | 28/4/38 | - | - | 4.5 |
| O. | 15/12/37 | ++ | - | 3.9 |
| | 23/12/37 | + | | 4.3 |
| | 5/1/38 | - | | 4.9 |
| | 25/1/38 | - | | 4.9 |

TABLE 28 (Contd.)

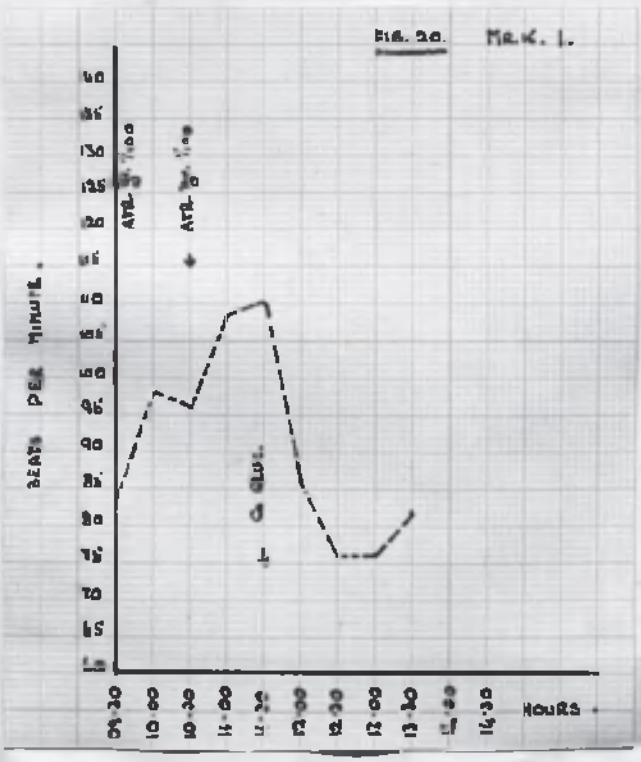
| Name | Date | Oedema | Cyanosis | Viscosity |
|---|---|---|---|---|
| P. | 9/5/38 | +++ | + | 3.5 |
| | 10/5/38 | +++ | + | 3.8 |
| | 11/5/38 | +++ | + | 3.5 |
| | 12/5/38 | ++ | + | 3.7 |
| | 15/5/38 | + | + | 3.9 |
| | 16/5/38 | - | - | 3.9 |
| | 1/7/38 | - | - | 3.0 |
| Q. | 25/5/38 | ++ | + | 4.9 |
| | 27/5/38 | ++ | + | 4.8 |
| | 28/5/38 | ++ | ++ | 5.4 |
| | 31/5/38 | +++ | ++ | 4.2 |
| R. | 31/1/38 | ++++ | ++ | 5.2 |
| | 2/2/38 | ++++ | ++ | 4.6 |
| | 3/2/38 | ++++ | ++ | 4.9 |
| S. | 12/2/38 | ++ | + | 3.3 |
| | 16/2/38 | + | - | 3.4 |
| | 10/3/38 | - | - | 3.9 |
| T. | 3/2/38 | + | ++ | 4.8 |
| | 9/3/38 | - | - | 4.5 |
| U. | 25/1/38 | - | - | 5.2 |
| | 28/1/38 | - | - | 5.2 |
| | 9/3/38 | - | - | 5.3 |
| V. | 4/3/38 | - | + | 4.2 |
| | 11/4/38 | | - | 3.9 |
| W. | 9/2/38 | +++ | ++ | 6.8 |
| | 3/3/38 | ++++ | ++ | 5.2 |
| | 24/3/38 | ++++ | ++ | 5.9 |
| X. | 15/2/38 | ++++ | +++ | 6.4 |
| | 16/2/38 | ++++ | ++ | 5.4 |
| | 21/2/38 | ++++ | +++ | 6.1 |
| Y. | 28/1/38 | - | - | 4.5 |
| | 31/1/38 | - | - | 4.6 |

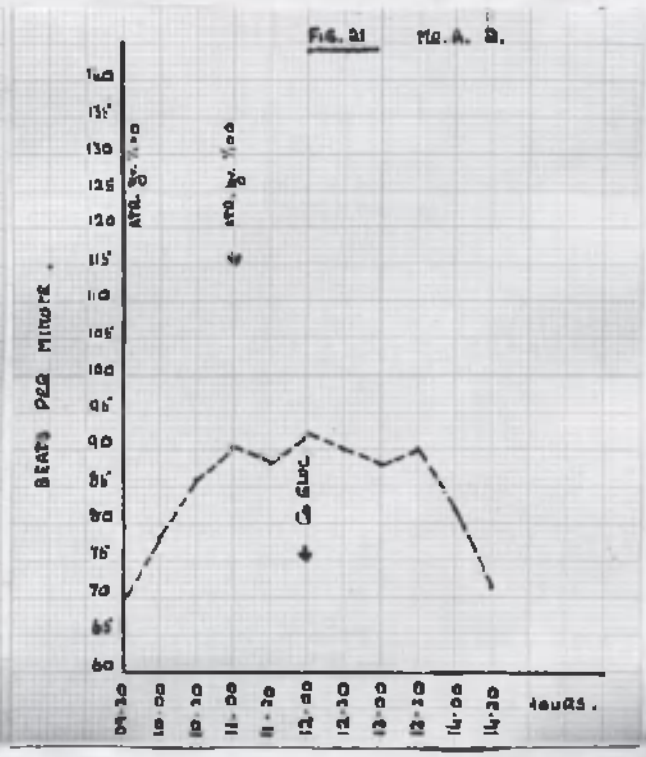
TABLE 28 (Contd.)

| Name | Date | Oedema | Cyanosis | Viscosity |
|---|---|---|---|---|
| Z. | 17/12/37 | ++++ | +++ | 4.3 |
| | 6/1/38 | +++ | +++ | 4.4 |
| | 25/1/38 | ++ | +++ | 4.9 |
| | 3/2/38 | - | ++ | 7.2 |
| | 11/2/38 | - | - | 4.9 |
| AB. | 4/1/38 | ++ | ++ | 7.0 |
| | 15/1/38 | - | ++ | 8.4 |
| | 24/1/38 | - | - | 5.2 |
| CD. | 4/1/38 | - | ++ | 4.6 |
| | 15/1/38 | | + | 4.3 |
| | 24/1/38 | | - | 3.7 |
| | 9/3/38 | | - | 5.0 |
| EF. | 4/4/38 | + | ++ | 4.7 |
| | 3/6/38 | - | + | 4.5 |
| GH. | 21/12/37 | - | +++ | 6.5 |
| | 22/12/37 | | ++ | 5.3 |
| | 4/1/38 | | ++ | 4.7 |
| | 15/1/38 | | ++ | 5.2 |
| | 24/1/38 | | + | 4.6 |
| | 9/3/38 | | - | 4.6 |
| IJ. | 11/1/38 | ++++ | - | 3.7 |
| | 12/1/38 | ++++ | | 3.7 |
| | 14/1/38 | +++ | | 3.9 |
| | 15/1/38 | +++ | | 3.9 |
| KL. | 29/12/37 | ++++ | ++ | 4.1 |
| | 28/1/38 | ++++ | ++ | 4.1 |
| MN. | 4/1/38 | - | + | 7.0 |
| | 3/6/38 | ++ | - | 5.5 |
| OP. | 25/5/38 | ++++ | + | 4.4 |
| | 24/6/38 | + | + | 5.2 |
| QR. | 10/1/38 | ++ | + | 5.2 |
| | 26/1/38 | ++ | + | 5.2 |

(c) In Part II, section (e), pages 39 and 40, three examples of the effect of the intravenous injection of calcium upon the atropinised heart are shown in figures. Two of these, Figs. 9 and 10, show absence of response to calcium in the direction of slowing of the heart rate, the other, Fig. 11, shows the slowing produced after incomplete atropinisation. Altogether fifteen patients were investigated in this way. The next twelve figures show the effects on the heart rate produced in the other twelve patients by the injection of calcium. In eight no slowing resulted, Figs. 21, 22, 23, 26, 28, 29, 30, and 31. In the other four slowing resulted from the injection - Figs. 20, 24, 25, and 27.

The conclusions to be drawn from these results are discussed in Part II, section (e).



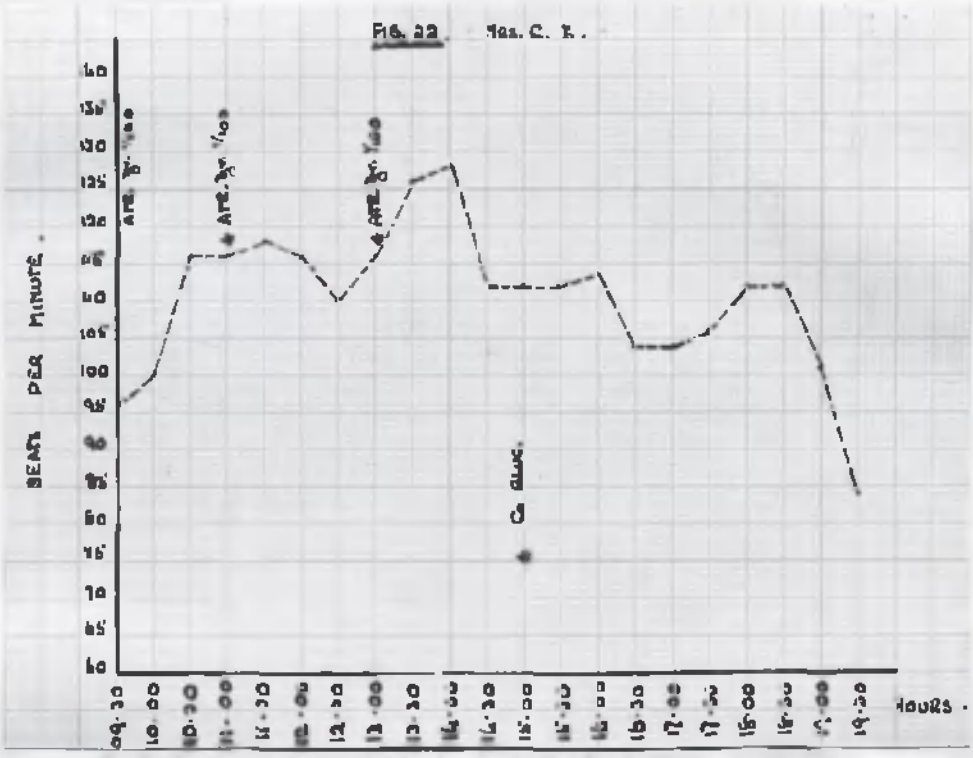


Fig. 22. Mrs. C. K.
BEATS PER MINUTE.
Ate. ½ Egg
Ate. ½ Egg
Ate. ½ Egg
G. Gluc.
HOURS.

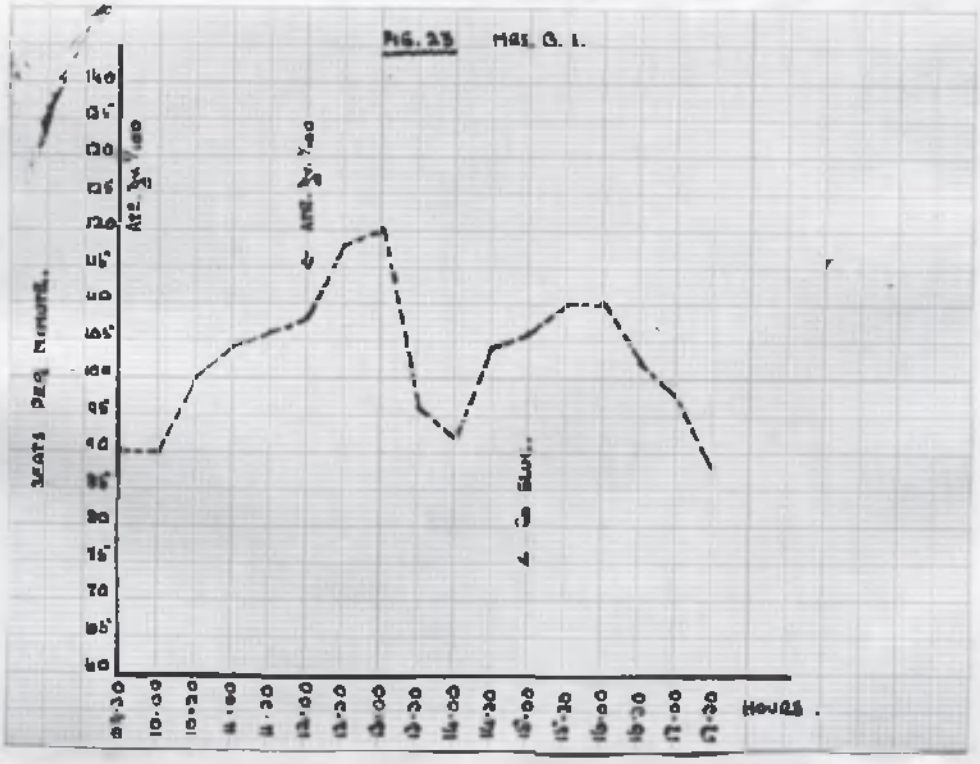


Fig. 23 Mrs. C. K.
BEATS PER MINUTE.
Ate. ½ Egg
Ate. ½ Egg
G. Gluc.
HOURS.

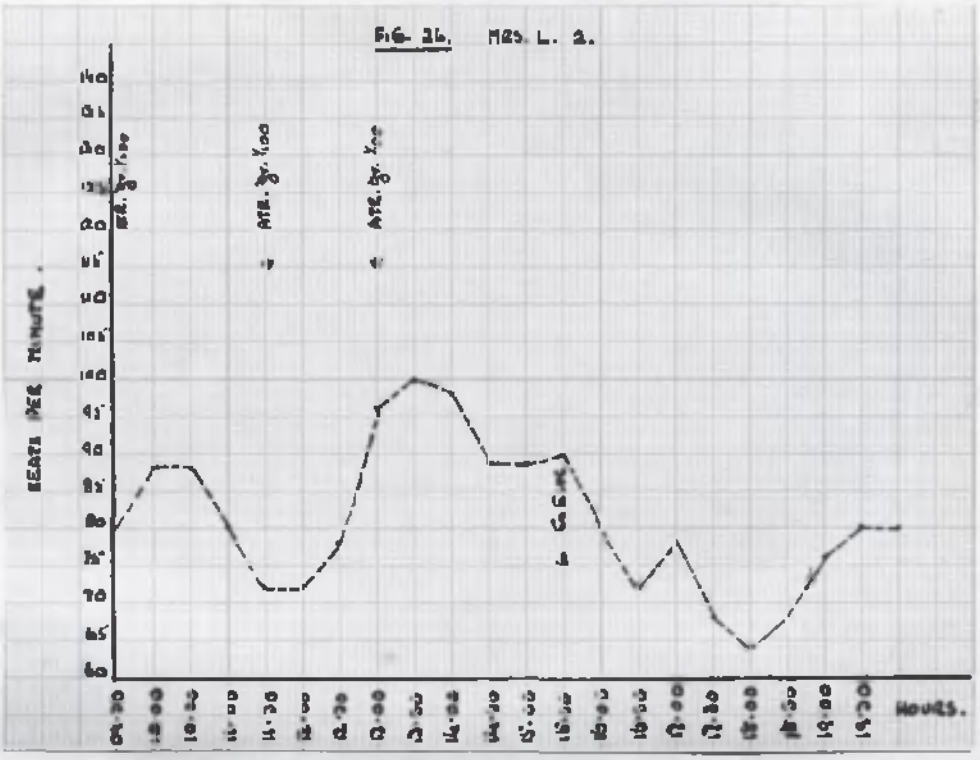


Fig. 24. Mrs. L. A.
BEATS PER MINUTE.
Ant. Syr. 1/100
Ant. Syr. 1/100
Ch Glue
HOURS.

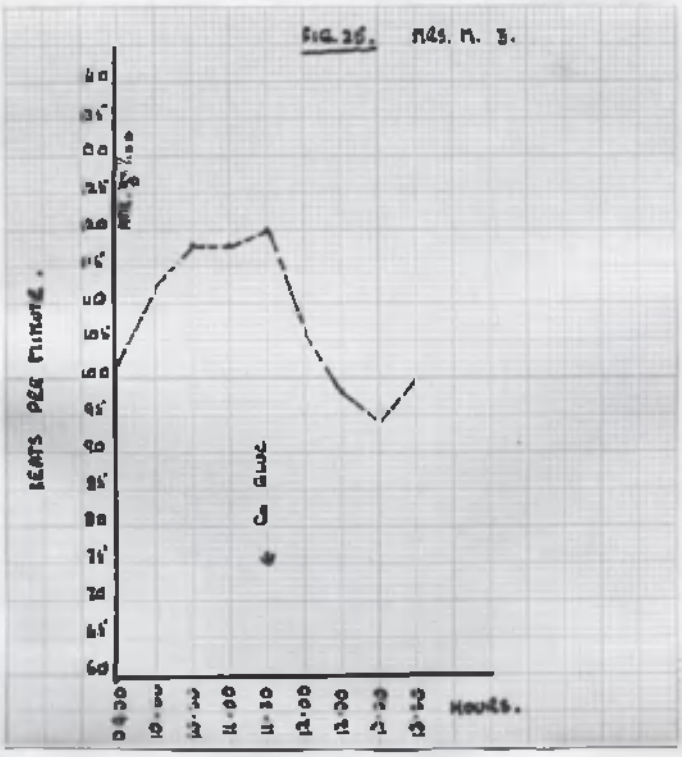


Fig. 25. Mrs. M. B.
BEATS PER MINUTE.
Ant. Syr. 1/100
Ch Glue
HOURS.

Fig. 26. Mrs. D. L.

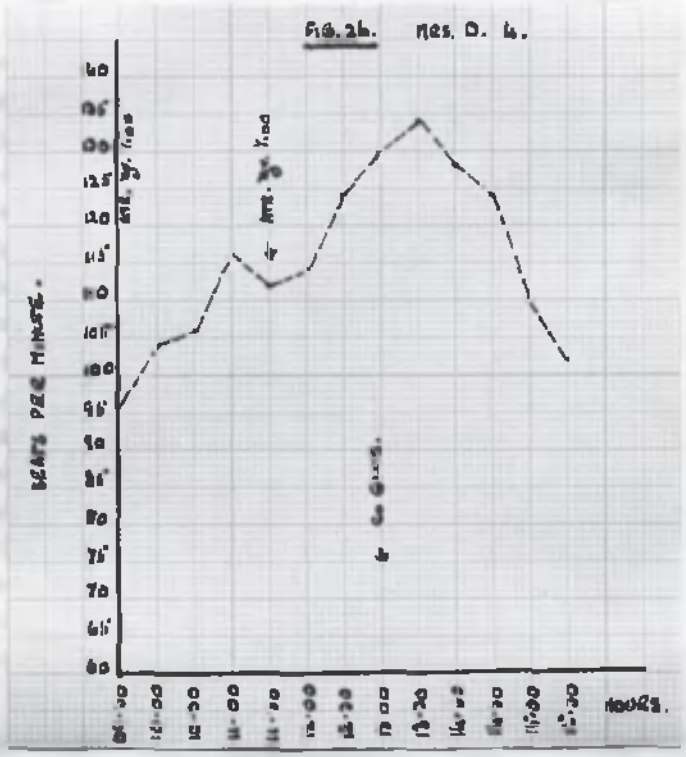
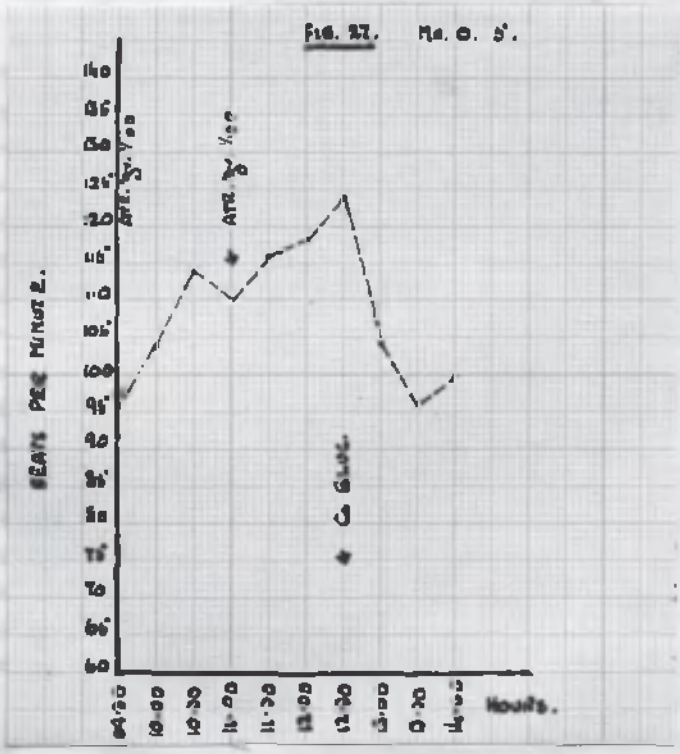



Fig. 27. Mr. D. S.



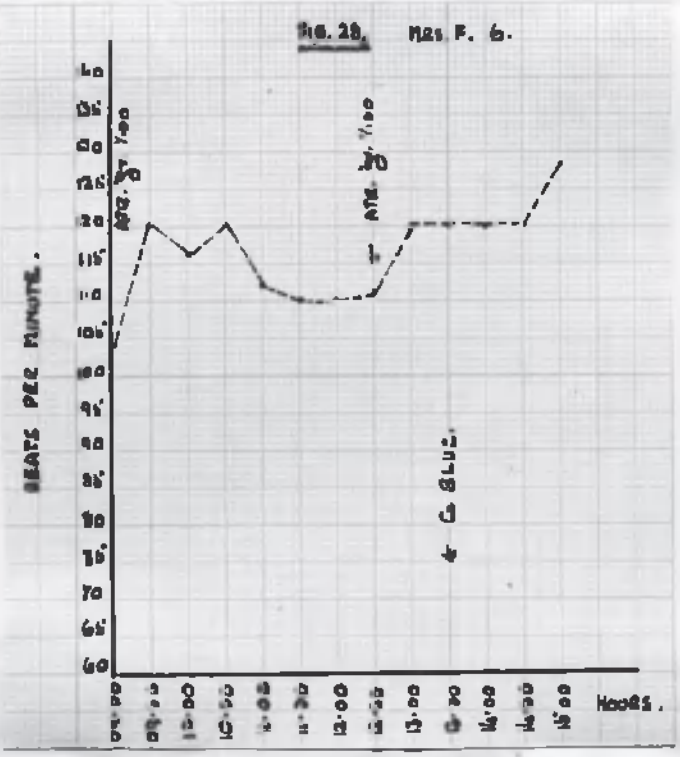


Fig. 28. Mrs. F. G.
BEATS PER MINUTE.
Hours.

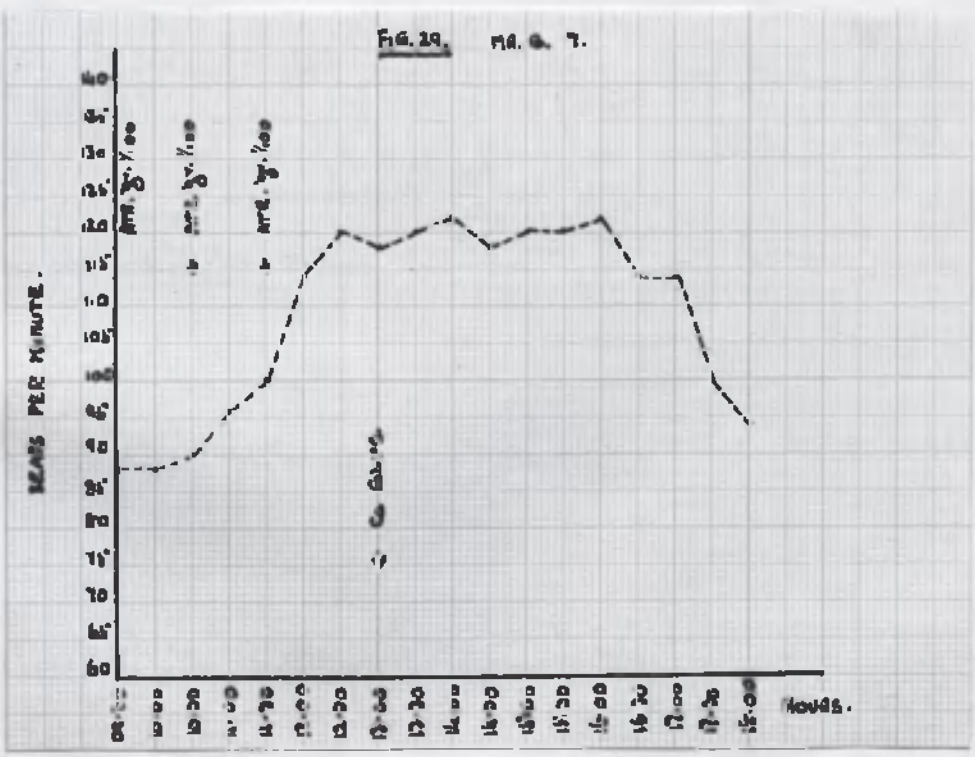


Fig. 29. Mr. G. T.
BEATS PER MINUTE.
Hours.

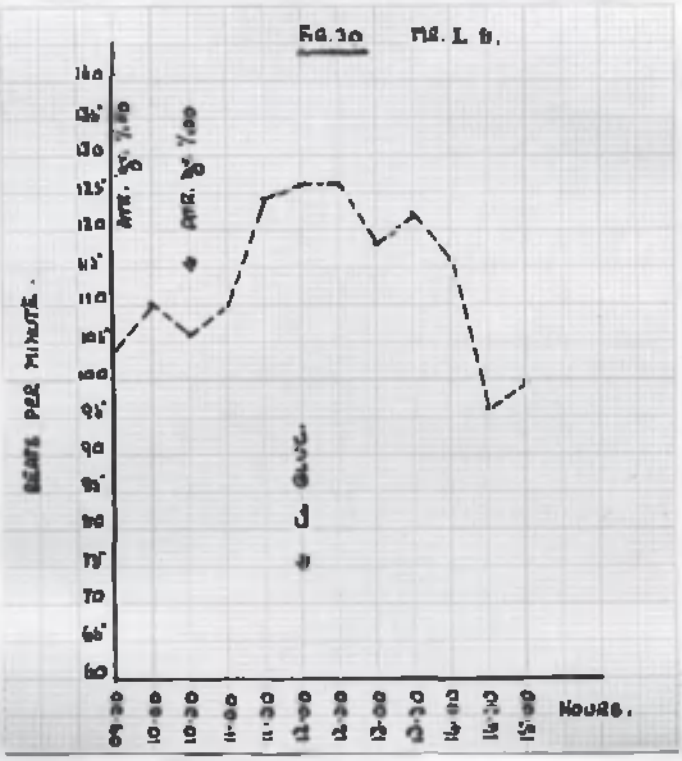


Fig.30 Pl. I. 9.
BEATS PER MINUTE.
Hours.
Art. Pr. Vas
Art. Pr. Vas
C. Carot.

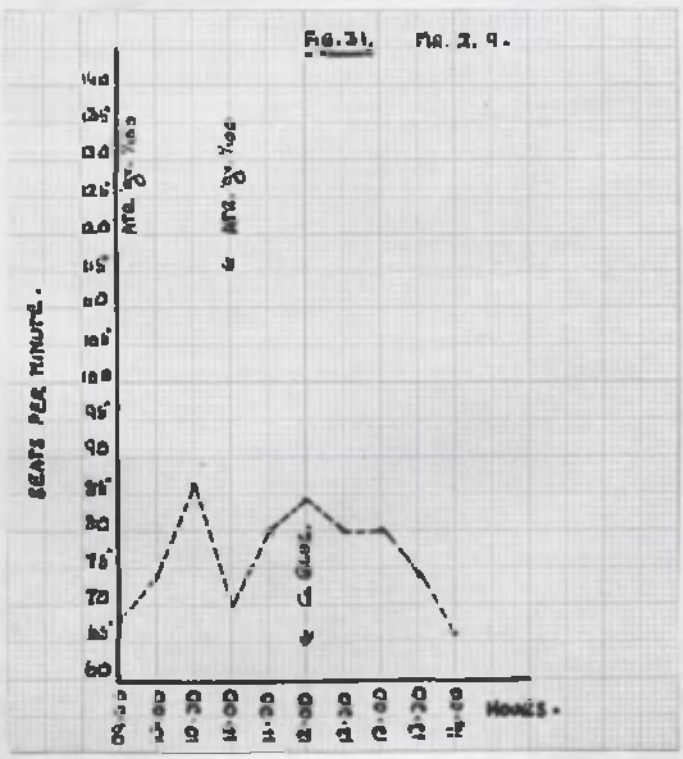


Fig.31. Pl. I. 9.
BEATS PER MINUTE.
Hours.
Art. Pr. Vas
Art. Pr. Vas
C. Carot.